# Diagnostic assessment of orofacial pain

Geerten-Has E. Tjakkes

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Research described in this thesis was conducted at the department of Oral and Maxillofacial Surgery and the Pain Center of the department of Anesthesiology in the University Medical Center Groningen.

This research project was supported by:
BOOA research grant

Publication of this thesis was supported by:

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Tandtechnisch Laboratorium Gerrit van Dijk

Cover: Betz (B.E. Tjakkes-Paas)
Design and lay-out: Jan Thie, Thie vormgevers, Groningen
Printing: Drukkerij van Denderen, Groningen

ISBN: 978-90-367-4614-4

## Stellingen behorende bij het proefschrift

# Diagnostic assessment of orofacial pain

1. Wanneer de criteria voor interne validiteit conform de Quality Assessment of Diagnostic Accuracy Studies (QUADAS) lijst worden gevolgd bij het opzetten van een wetenschappelijk onderzoek in het domein 'diagnostiek', is de kans groot dat deze studie wordt geïncludeerd in systematische reviews en dus zal bijdragen aan de beschikbare 'evidence'. (dit proefschrift)

2. Het pijnverminderend effect van intra-articulaire anesthesie van het kaakgewricht bij patiënten met preauriculaire pijn moet worden geïnterpreteerd tegen de achtergrond van het placebo-effect. (dit proefschrift)

3. Een placebo is niet niks. (dit proefschrift)

4. Optimalisatie van de farmacologische test ten behoeve van de diagnostiek van chronische pijn zal primair gericht moeten zijn op vermogen nociceptieve van niet-nociceptieve pijn te onderscheiden. (dit proefschrift)

5. Work expands so as to fill the time available for its completion. (C.N. Parkinson 1955)

6. Het diagnosticeren en succesvol behandelen van een somatische aandoening sluit aanwezigheid van een psychologische component niet uit.

7. De term "studie medicijnen" zou toepasselijker zijn voor de studie farmacie dan voor de geneeskundestudie.

8. Tandartsen die zich bij het verantwoorden van hun handelen uitsluitend beroepen op "jarenlange ervaring", maskeren daarmee gebrek aan theoretische kennis.

9. Geld lenen is omgekeerd (en duur) sparen.

10. Het grote aantal talentenjachten op televisie vermindert de waarde van het winnen ervan.

11. In theorie liggen praktijk en theorie dicht bij elkaar, in de praktijk is dat vaak niet zo.

12. Een periodiek mondonderzoek zonder parodontale screening is een kunstfout.

13. Een stelling over stellingen begrijpt niet iedereen.

Geerten-Has E. Tjakkes, 17 november 2010

RIJKSUNIVERSITEIT GRONINGEN

# Diagnostic assessment of orofacial pain

Proefschrift

ter verkrijging van het doctoraat in de
Medische Wetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus, dr. F. Zwarts,
in het openbaar te verdedigen op
woensdag 17 november 2010
om 14.45 uur

door

Geerten-Has Egge Tjakkes
geboren op 27 februari 1979
te Assen

| | |
|---|---|
| Promotores: | prof. dr. B. Stegenga<br>prof. dr. L.G.M. de Bont |
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## Contents

# Introduction

# 1

## Introduction

The International Association for the Study of Pain (IASP) has defined pain as *'an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage'* (Merskey and Bogduk, 1994).

According to this definition, there are two main issues associated with pain, i.e.:
1. tissue damage is involved.
2. it refers to an individual experience.

This emphasizes the importance of a bi-axial approach of pain, including a physical as well as a psychosocial axis (Okeson, 2005).

Chronic pain is usually defined as pain without apparent biologic value that has persisted beyond the normal tissue healing time (which is about 3 months) (Zakrzewska and Harrison, 2002; Palla, 2006). This term is used in contrast with acute pain, which is pain due to tissue damage, infection or inflammation (Sternbach, 1974).

Chronic pain may develop from an ineffectively or inadequately (albeit unintentionally) treated acute pain condition. A coinciding problem is that, when pain persists over time, neuroplastic changes may occur and psychosocial behavioral changes tend to become more influential. Chronicity of pain involves anatomical, physiological, psychological, neurochemical, and genetic changes that make evaluation difficult.

Signals from the nociceptors terminate in the caudal nucleus of the medullar trigeminal system. After prolonged nociceptive input, the dendritic nerve terminals release chemical mediators, such as glutamate, substance-P, and calcitonin gene-related peptide. These mediators modulate the excitability of neuronal membranes in the dorsal horn of the spinal cord and medulla, leading to sensitization of the second order neurones. This process is termed 'central sensitization' (Dubner and Ren 2004). The prolonged signalling cascades in second-order nociceptive neurons elicited by subsequent close-spaced stimuli lead to an increase in the action potential discharge, a phenomenon referred to as "windup" (Salter 2004). In addition to an increase in the expression of excitatory transmitters, inhibitory mechanisms may be suppressed, thus contributing to sensitization. Recently the influence of non-neuronal (glial) cells has been suggested as a point of focus in neuroplasticity. Hyperactive glial cells appear to be involved in the modulation of trigeminal spinal subnucleus caudalis (Vc) and spinal dorsal horn activity after inflammation or peripheral nerve injury (Okada-Ogawa et al., 2009). Related to this mechanism, the enzyme aconitase and astroglial-dependent glutamine supply has been suggested to be relevant in sustaining enhanced neuronal activity related to chronic pain mechanisms (Okada-Ogawa et al., 2009).

Clinically, central sensitization may give rise to secondary hyperalgesia, i.e. a lowering of the pain threshold and increased response to noxious stimuli (Merskey and Bogduk,

1994). Allodynia is another phenomenon associated with sensitization, which is characterized by a painful and persistent pain response to a normally non-noxious stimulus (Henry, 2004). In addition to the aforementioned hyperphenomena, sensory deficits such as hypesthesia (decreased sensitivity to stimulation excluding the special senses), hypalgesia (diminished pain in response to a normally painful stimulus), as well as paresthesia (an abnormal sensation, whether spontaneous or evoked) and dysesthesia (an unpleasant abnormal sensation, whether spontaneous or evoked) may occur (Merskey and Bogduk, 1994).

The neuroplastic changes may also lead to different kinds of heterotopic pain, i.e. pain that is felt in another area than the location of the source. In projected pain the site where the pain is felt lies distally in the distribution of the same nerve as the source of pain. Referred pain is also felt at another site than the source, but this site does not necessarily lie within the distribution of the same nerve, but rather at the same segmental level (Okeson, 2005).

*Biaxial diagnosis of pain conditions*

Currently, it is generally agreed to establish a pain diagnosis in a biaxial system. Axis I concerns the somatic diagnosis (related to the underlying tissue damage), and axis II expresses the functional and psychosocial impact of the pain experience on the patient. As chronic pain is unrelenting, stress, environmental, and affective factors may likely superimpose on the effects of the damaged tissue(s) and, therefore, likely contribute to the perceived intensity and persistence of pain (Loeser and Melzack, 1999; Dworkin, 2001).

In most common orofacial pain conditions, establishing an axis I diagnosis is relatively easy, and the source of pain may be identified based on the patient's complaints and using routine diagnostic tests, such as provocation and/or anesthesia tests. It should be noted that psychological factors play a role in all types of pain, irrespective of its duration. In longer lasting and chronic pain conditions, however, psychosocial factors become more prominent and even may dominate and obscure the clinical presentation. A shift in the origin of pain from somatosensory input to affective, cognitive, and behavioural inputs of pain may take place (Okeson, 2005). After a more extended duration of pain, either with a constant, decreased or even a disappeared somatosensory input, the level of suffering is likely to increase. In cases where axis II factors dominate, this should be a serious and significant part of the diagnostic assessment as well as of the therapy, even more than in (sub)acute situations. This is confirmed by the finding that psychological factors are better predictors of treatment outcome in patients with chronic pain conditions than somatic findings (Turk and Okifuji, 2002; Dworkin, 2006).

*Health beliefs*

During the past decades, there has been an enormous shift in health beliefs (of patients and clinicians), such as the importance of a certain life style (alcohol consumption, tobacco smoking, food consumption, physical exercise) in relation with several diseases (e.g. cancer, heart diseases) (World Cancer Research Fund, 2007). In contrast, most pain

patients (as well as many doctors) still tend to approach chronic pain from a biomedical point of view (Feinmann, 2004). The inability to identify the cause of or to offer a cure for the pain is often interpreted as the failure of the examination or tests used to establish a diagnosis or as insufficient competence of the clinician to deal with the problem. This may either lead to repetition of examinations or tests or to visiting other clinicians, thus contributing to "medical shopping" behaviour (Feinmann, 2004). In turn this may lead to a frustrated patient, who is led to think that the medical system is unable to cure him or her. This may lead to a change in attitude of the patient towards the clinician, which in turn may be interpreted by the clinician as underlying psychopathology. Biomedically oriented clinicians consider attention for the effect of the pain on the patient's daily life as being unimportant as it is not biology-based. Introverted interest in psychological factors may lead to the belief that the pain is imaginary or made up by the patient (Dworkin, 2001). This complicates and frustrates the patient-doctor-relationship as well as the outcome of further assessment and treatment of the chronic (orofacial) pain patient.

The state of the current knowledge of orofacial pain is, however, hardly represented by the current practice in oral health care; outdated diagnostic procedures are still used; theories explaining diseases that have been disproved are still communicated to patients and inappropriate or harming treatments are still offered (Greene, 2001; Klasser and Greene, 2009).

*Classification of pain conditions*

In (medical) science, classification systems are thought to be essential for epidemiological studies, clinical decision making, treatment planning, the indication of treatment, and the evaluation of treatment efficacy (Zakrzewska, 2002). There is, however, a continuing controversy in the classification and definitions of disease (Scadding, 1996). One part of the controversy lies in the distinction between realists, who are in this context referred to as "essentialists", and "nominalists". The essentialists' definition starts with "X is…" which presupposes the existence of something that can be identified as X. On the other hand, nominalists typically would say "X refers to …", which explains the sort of observations that are required to test the truth of sentences, including hypotheses, in which X occurs. (Scadding, 1996). So in nominalism, a classification is based on the resemblance of signs and symptoms in a group of patients. In relation to this, Turk and Rudy have made the distinction between pain classifications based on theoretical background and those based on empirism. (Turk and Rudy, 1992)

In a theoretical classification, a group of signs and symptoms are thought to be unique for a disease and, therefore, able to differentiate between subjects. Examples of classification systems using a theoretical classification for pain in the orofacial region include classifications of the International Headache Society (IHS), the International Association for the Study of Pain (IASP), the American Association for Orofacial Pain (AAOP), and the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD). In the empirical approach, a set of variables which characterizes a group is identified. Examples of this approach are instruments as the Symptom Checklist SCL-90 and the McGill

Pain Questionnaire (MPQ) and the West-Haven Yale Multidimensional Pain Inventory (WHYMPI or MPI). The MPI was used in a group of patients with temporomandibular disorders (TMD). After cluster analysis, three groups could be indentified and were labeled "dysfunctional", "interpersonal distressed" and "adaptive copers" (Rudy et al., 1989). So apparently, using an empirically derived classification system was able to (alternatively) classify TMD patients, irrespective of the origin or nature of the disease.

Remarkably, the theoretically based classification systems are more frequently used than the empirical classification systems. With regard to the orofacial area, the classification system of the IASP (Merskey and Bogduk, 1994) results in a collection of groups of so called "relatively localized syndromes of the head and neck". The pain conditions are classified by pain characteristics, i.e. main features, pathology, course, complications, and differential diagnosis where possible.

The IHS has introduced a classification system where facial pain diagnoses, mainly related to headaches in the broadest sense, are described by diagnostic criteria obtained by consensus (Olesen, 2004). The pain conditions are classified according to phenomenology, and with each condition a description of its characteristics is provided together with diagnostic criteria required to be satisfied. With regard to orofacial pain, this classification system has been extended by the AAOP (McNeill, 1993; Okeson, 1996; de Leeuw, 2009), which is widely used by workers in this field.

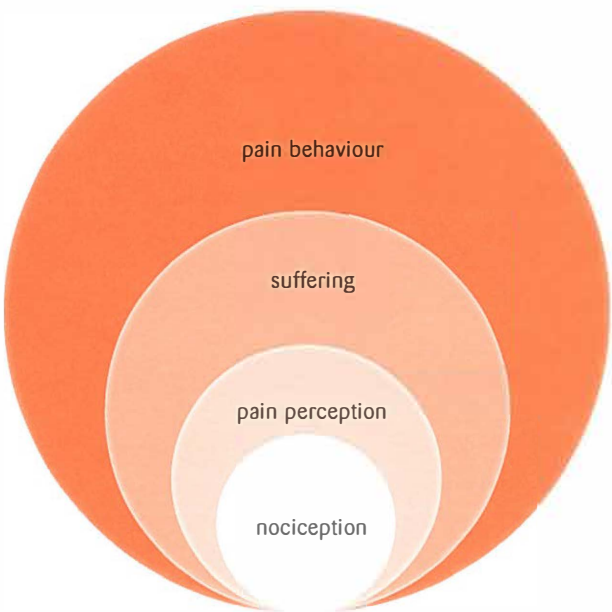
It is generally agreed that pain in the orofacial region that has become chronic is a complex problem for the patient as well as for the clinician. The IHS, IASP, AAOP and RDC/TMD criteria represent most acute conditions, but chronic pain problems only partly. However, this may be due to obscure presentation and symptoms, some chronic pains cannot be classified using these criteria. This is illustrated by the terms used in the literature to designate these problems, i.e. 'atypical facial pain', 'atypical odontalgia', 'chronic pain syndrome', 'idiopathic chronic (orofacial) pain'. It is not clear whether these pain types are distinct or that they show resemblance to each other or are distinguished by location (Aggarwal et al, 2007). One of the characteristic features is that these conditions are complex and are (often) diagnosed per exclusionem. Especially in these cases, information gained by history taking alone may be insufficient and further diagnostic information is desirable.

## General aim of this thesis

As can be derived from the aforementioned, chronic pain is a complex matter. Pain is often considered as a symptom of a disease, and this is likely the case in acute situations. However, when severe or persistent, the underlying tissue damage may resolve while the pain persists and becomes chronic. In these cases, the pain experience has become the main component of the condition. Chronic pain presents with its own symptoms, such as disability, depression and sleep disturbances and the pain should be considered as the disease itself (Niv and Devor, 2004). Nevertheless, when a patient attends the clinician with a chronic pain problem, the pain is often primarily considered as a symptom of underlying disease and the patient often expects to be diagnosed and subsequently treated accordingly. This is the key of the problem with which the clinician is faced.

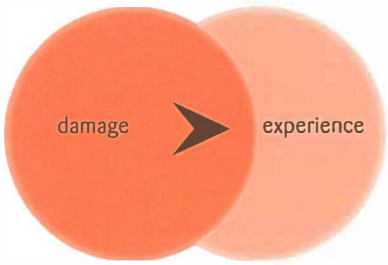
*Current classification and assessment procedures may be unable to elucidate causes or underlying mechanisms of pain and have therefore not led to a diagnosis and subsequent satisfactory treatment. Alternative diagnostic procedures may give valuable insight in the patient's pain problem.*

In relation to the bi-axial approach, Loeser developed a pain model, which illustrates in a simplified manner how different dimensions of pain may be imagined. These dimensions are illustrated by a series of overlapping circles (Loeser and Black, 1975). These four different dimensions do not necessarily occur in every body, nor do they occur to the same extent. In fact, the relative size of the circles in the model may vary per patient. Therefore, the assessment of the influence and importance of these different levels in orofacial pain patients cannot be grasped within single method and requires different approaches.

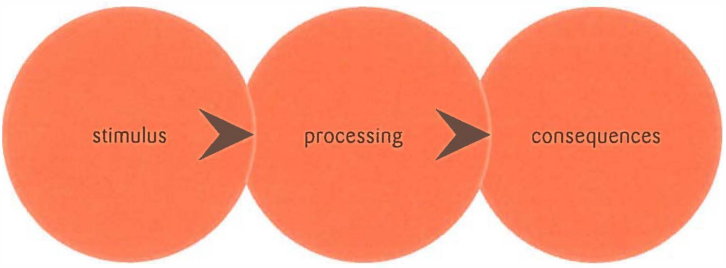


The smallest circle represents the noxious stimulus (nociception; activation of nerve fibers). The surrounding circle is referred to as perception of pain, which is influenced by phenomena such as hyperalgesia, allodynia, hypesthesia, hypalgesia, paresthesia and dysesthesia. Pain perception frequently results from an underlying noxious stimulus (nociceptive pain), but may also be generated by lesions within the peripheral or central nervous system. (Loeser and Melzack, 1999). Pain perception, especially when pain exists over a longer period of time, may lead to suffering. Suffering is a response induced by pain, but it is also induced by e.g. fear, anxiety, stress, and other psychological states. In turn, the suffering affects the patients' pain behaviour. Pain behaviour is observable and quantifiable.

In an adapted, simplified version of this model, pain could be illustrated as follows:




This figure shows that pain originates from damage. Whether the damage is currently present or not, in both situations the processing of damage will eventually lead to pain experience. So, pain involves (originally) a stimulus, which after processing has consequences, such as psychological and social ones. The Stimulus-Processing-Consequences-model (SPC-model) illustrates this:




In assessing patients with pain, the focus could be on the origin of the pain, but alternatively, it could be on one or more of the abovementioned three SPC levels. The (location of the) stimulus could be targeted by means by provocation, but alternatively also by local anesthesia. The effect of pharmacological agents could be of help in the assessment of patients, giving more insight in the pain problem. We refer to the diagnosis of pain using pharmacological agents as pharmacodiagnostics. So, pharmacodiagnostics can be per-

formed locally but also systemically. Theoretically, both the levels stimulus and processing can also be affected by systemic pharmacodiagnostics, providing additional information for subsequent treatment. Chronic pain has a functional as well as a psychosocial impact, implying significant psychological and social consequences patients' experience, which is reflected by the quality of life (QoL). Attention in diagnostic assessment should therefore also be given on the third level, the consequences. In this, QoL could therefore be the focus in examination and assessment of chronic pain patients.

In short, the general aim of this thesis is to enhance the diagnostic assessment in chronic orofacial pain, by focusing on three basic components of pain, i.e. the stimulus, the processing of the pain signal, and the consequences of pain.

**Specific aims**

In order to facilitate the diagnostic process in orofacial pain patients, numerous diagnostic tests have already been suggested and used. However, the evidence for diagnostic validity and their clinical relevance as well as the feasibility of these tests differ and are sometimes even lacking. Whether a test was properly studied, under which conditions, is suitable for use and what can be concluded from it remains unclear.

*To provide an overall overview and appraisal of the currently used and qualitatively well-studied diagnostic tools in chronic orofacial pain, a systematic review of the current literature is presented in chapter 2.*

Orofacial pain refers to pain originating below the orbitomeatal line, above the neck, and anterior to the ears (Zakrzewska 1999). Most commonly, orofacial pain originates from the dentoalveolar area, and usually involves an inflammatory response related to an infection or traumatic injury. The most common cause for orofacial pain is dental pain, e.g. caused by caries, pulpitis, or periodontal disorders. The prevalence of dental pain is associated with the prevalence of caries, which, in turn, depends on the diet, social class, fluoride intake, and oral hygiene (LeResche 2001). In a community-based study, MacFarlane et al. found an overall orofacial pain prevalence of 26% (MacFarlane et al., 2002). For pain in the temporomandibular area, which represents another common group of orofacial pain complaints, an average estimated prevalence of 10% was found (LeResche, 1997). After a proper diagnosis is made in these conditions, subsequent treatment may be initiated and will, in most cases, be successful.

In the (sub)acute cases, such as the aforementioned painful conditions, the diagnostic process will be relatively straightforward, as the presentation of the complaints is usually characteristic for these conditions. In these cases, the importance and influence of the nociceptive level will be relatively large and the emphasis in diagnosis and treatment will be mainly (but not exclusively) on this dimension.

In the process of *identification of the structure with tissue damage* and from which the pain emanates, provocation-tests are usually performed. When the site and source of the

pain are not the same (e.g. in secondary pain), local provocation of the site of pain will not increase the pain, whereas local provocation of the source of pain will increase the pain, not only at the source of pain but also at the site (Okeson, 2005). In addition, local anesthesia can be used in establishing the source of pain. When the site and source are not the same, local anesthetic blocking of the site of pain will not decrease the pain, and local anesthetic blocking of the source of pain will decrease the pain at the source as well as the site (Okeson, 2005). This technique has been previously propagated, for example for trigger points in myofascial pain conditions. Also in patients where the pain is suspected to be of pulpal origin, local anesthesia is frequently used to establish the site of pain. In patients with temporomandibular disorders, several tests that focus on provocation have been described (Visscher et al., 2009). In these patients, administration of local anesthesia could aid in establishing the source of pain. However, the distinguishing capacity of intra-articular temporomandibular joint (TMJ) anesthesia has never been studied, and the validity of such a test has never been established.

*Chapter 3 focuses on pharmacodiagnostics. In chapter 3.1, a study is described with the aim of evaluating the distinguishing ability of intra-articular anesthesia from placebo in orofacial pain patients with pain located in the TMJ region, aiming at a validation of intra-articular anesthesia injection as a diagnostic test for pain in the TMJ region.*

Many factors have been suggested to be associated with (chronic) pain, most of which are addressed in history taking: premonitory symptoms, precipitating factors, onset of the pain, alleviating factors, environmental as well as social factors, family history, psychological and psychiatric history and medication use (Zakrzewska, 2002). Care should be taken not to jump to conclusions too soon. All collected information should be carefully weighed and integrated. Valuable additional information is gained from physical examination. Based on the collected information, a differential diagnosis can be made. In many cases, the combination of the history and the physical examination provides sufficient information to arrive at a definitive diagnosis or limited differential diagnosis. There is a need for more insight when the available information in chronic patients who have undergone extensive history taking, physical examinations and additional diagnostic tests which did not yield sufficient information to come to a diagnosis or classification.

Based on pain research that has been carried out during the past decade, different *pain processing mechanisms* have been described. The most common and prominent pain mechanisms include nociceptive pain, neuropathic pain, and sympathetically maintained pain (SMP). In chronic pain patients, knowledge of the mechanism(s) underlying or contributing to the clinical pain presentation may be valuable in further assessment and treatment. Therefore it seems legitimate to use pharmacological agents specifically aiming at these mechanisms, in order to help to disentangle their effects. In this form of pharmacodiagnostics, several pharmacological agents are used, in order to classify patients based on their response to administered agents.

*In chapter 3.2 pain diagnosis using pharmacological agents has been studied in different pain groups. Focusing on orofacial pain patients, a preliminary intravenous diagnostic test was developed and applied in the pain clinic. The results of performed pharmacodiagnostic tests and its potential distinctive ability were evaluated retrospectively, and the results are presented in chapter 3.2. Based on these result, the test was slightly modified. In chapter 3.3 the results of an analysis of its distinguishing ability between nociceptive pain, neuropathic pain, and sympathetically maintained pain are presented. The potential predictive validity of the test was studied by testing patients of whom the underlying pain mechanism (i.e. nociceptive, neuropathic and sympathetically maintained) was probable.*

The *consequences* of chronic pain may be far reaching, especially for the patient's quality of life. When the patient's daily life becomes dictated by pain, psychological changes and restrictions in lifestyle it is likely to result in limited capabilities. Recognition and acknowledgement of these factors may enhance the assessment, aid in the diagnostic process, and guide management of chronic orofacial pain patients. It is generally agreed, that the longer pain persists, the more it influences QoL. Whether this is really the case and, if so, to what extent, is still not clear. In addition, assessment of QoL can take place using standardized tools, although in chronic pain patients predetermined measures may be insufficient to incorporate all factors that determine an individual's QoL. Therefore, an alternative assessment method may be of additional value in QoL appraisal.

*Chapter 4 addresses the assessment of health-related quality of life (HRQoL) in patients with chronic orofacial pain. The aims of the study presented in chapter 4.1 were to assess whether the HRQoL is decreased in chronic orofacial pain patients as compared to the general population, to study the differences in HRQoL between groups with different symptom duration, and to study the effect of the duration of symptoms on HRQoL. An exploration of an individualized approach in quality of life assessment in orofacial pain patients revealed additional information compared to the information obtained from standardized quality of life assessment. This study is presented in chapter 4.2.*

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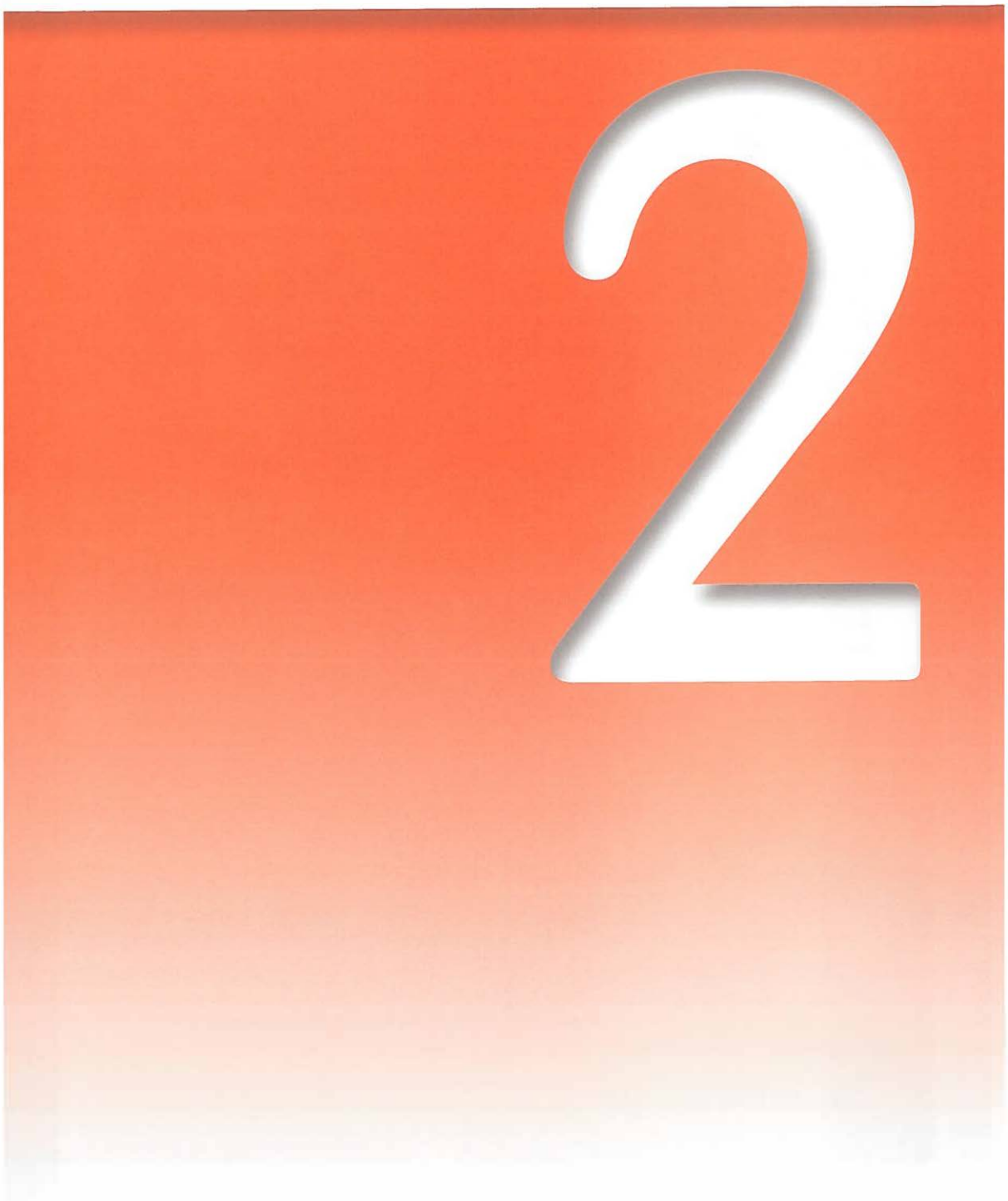
# Diagnostic tests in orofacial pain patients. A systematic review

*This chapter is based on: Diagnostic tests in orofacial pain patients. A systematic review. Tjakkes GH, Huddleston Slater JJR, Van Wijhe M, Stegenga B, submitted.*



## Abstract

**Aims:** In patients with persistent pain in the orofacial region, changes in the nervous system have been shown to occur. In addition, psychosocial factors become more prominent. This has consequences for the diagnostic process and subsequent treatment of these patients. To assist the diagnostic process, several tools are available. The aim of this paper was to systematically assess the quality of clinical diagnostic tests currently performed in patients with persistent orofacial pain and, subsequently, to assess the clinical feasibility of these tests in patients with persistent pain.

**Methods:** A literature search was performed, aiming at studies investigating diagnostic tests for different types of orofacial pain. Relevant studies were analyzed using a quality assessment tool for diagnostic accuracy (QUADAS). This tool consists of 14 items referring to internal validity. Studies scoring more than 50% of these items were further assessed for their clinical relevance and applicability.

**Results:** When assessing the quality of the existing literature using a developed quality assessment tool, 15 articles were found to be of sufficient methodological quality. Especially studies concerning the use of magnetic resonance angiography in trigeminus neuralgia patients and the use of magnetic resonance imaging in patients with temporomandibular arthralgia are well represented in the literature.

**Discussion:** When literature concerning the diagnostic tests in orofacial pain conditions is reviewed and qualitatively appraised, only a minority remains, which concerns mainly well defined orofacial pain types.

## Introduction

In medical and dental practices, orofacial pain is a common reason for patients to seek treatment. To make a diagnosis in these patients, a full pain history is mandatory. The history should include the character, the mode of onset, the location, the duration as well as the periodicity, the referral pattern, and the severity of the pain. In addition, associated factors should be included: premonitory symptoms, precipitating factors, onset, alleviating factors, environmental as well as social factors, family history, psychological and psychiatric history and medication use (Zakrzewska and Harrison, 2002). In combination with the physical examination, this will in the majority of cases provide sufficient information to arrive at a diagnosis. However, in chronic orofacial pain cases, despite a thorough history and physical examination, the cause and mechanism often remain unclear. These conditions are currently referred to as chronic idiopathic orofacial pain.

Persistent pain in the orofacial region has been shown to give rise to changes in the nervous system (Sessle, 2000). These neuroplastic changes lead to altered pain perceptions such as referred pain, hyperalgesia, and allodynia. In addition, the effects of psychosocial factors become more prominent (Dworkin, 2006). This complicates the diagnostic process and subsequent treatment of these patients. For the diagnostic classification of chronic idiopathic orofacial pain patients, the oral history and physical examination are frequently insufficient; hence additional investigations are required. A large variety of diagnostic tools have been developed and applied. The scientific rationale for their use is often inconclusive, and often based on clinical experience or what seems to be common sense. Therefore, in order to study the current diagnostic methods and their applicability in patients with persistent orofacial pain, it seemed worthwhile to systematically review the literature for the available evidence.

The primary aim was to systematically review the literature with regard to diagnostic tests performed in patients with orofacial pain. Studies of satisfactory methodological quality were used to assess the clinical quality and applicability of the tests.

## Methods

### Search methods for identification of studies

*Electronic search:*

A literature search was executed in Medline using Pubmed (Pubmed 1957-2008) and the Cochrane Database of Systematic Reviews. In table 1 the search terms are shown. For the purpose of identifying diagnostic publications, a methodological filter was used adapted from a recently published search string for publications concerning diagnostic accuracy (Devillé et al., 2002). To retrieve literature concerning diagnostic tests studied in a randomized controlled design, a search string for randomized controlled trials (RCT's) was also used (Glanville et al., 2006) (figure 1). Articles in English, French, German and Dutch were selected.

*Searching other resources*

A manual cross-reference search of eligible studies was performed to find other relevant studies.

### Criteria for considering studies for this review

The title, abstract, and key words of identified studies were screened independently by one reviewer for relevance to the systematic review. We have considered diagnostic studies in which the primary goal was to compare an index test with a reference test. Case reports, narrative reviews, editorials, letters, commentaries, duplicate publications of the same patient population, case-control trials and papers studying the efficacy of treatment were excluded. To establish a broad search, no a priori restrictions with regard to the orofacial pain condition were used, and all studies carried out in primary, secondary and tertiary care were included. Studies using healthy volunteers with experimental pain were excluded.

### Assessment of methodological quality

The quality of each study was assessed by two authors (GHT and JHS), using the Quality Assessment of Diagnostic Accuracy Studies list (QUADAS) (Whiting et al., 2003). This checklist consists of 14 items that refer to internal validity (table 2). Each item was scored as "yes" (positive assessment), "no" (negative assessment) or "unclear" (insufficient information), based on the description in the user's guide for the QUADAS. In order to obtain qualitatively adequate studies, we argued that studies scoring "yes" in more than half (7) of the questions could be included for further appraisal.

Inter-observer agreement (kappa) was calculated for agreement in inclusion of appropriate studies (Landis and Koch, 1977). Disagreement was be resolved by a consensus discussion or, if necessary by a third party (BS).

### Data extraction

Two reviewers independently extracted data from the included studies and considered the following items: bibliographic details, details of the study setting, characteristics of study population, frequency and course of the tests, baseline and outcome measures. Uncertainties on data extraction were resolved by discussion between the reviewers.

Table 1. Used search terms

**Pain diagnosis**

"Facial Pain"[Mesh] OR "Facial Neuralgia"[Mesh] OR "Toothache"[Mesh] OR "Trigeminal Neuralgia"[Mesh] "Glossopharyngeal Nerve Diseases"[Mesh] OR "Burning Mouth Syndrome"[Mesh] OR "Temporomandibular Joint Dysfunction Syndrome"[Mesh] OR facial neuralgia OR facial pain OR orofacial pain OR odontalgia OR trigeminal pain OR trigeminal neuralgia OR trigeminal postherpetic neuralgia OR trigeminal neuropathic pain OR glossopharyngeal neuralgia OR burning mouth OR temporomandibular joint pain OR craniomandibular pain OR TMJ pain

**Search string for diagnostic studies**

(((((("sensitivity and specificity"[All Fields] OR "sensitivity and specificity/standards"[All Fields]) OR "specificity"[All Fields]) OR "screening"[All Fields]) OR "false positive"[All Fields]) OR "false negative"[All Fields]) OR "accuracy"[All Fields]) OR ((((("predictive value"[All Fields] OR "predictive value of tests"[All Fields]) OR "predictive value of tests/standards"[All Fields]) OR "predictive values"[All Fields]) OR "predictive values of tests"[All Fields])) OR (("reference value"[All Fields] OR "reference values"[All Fields]) OR "reference values/standards"[All Fields]) OR (((((((("roc"[All Fields] OR "roc analyses"[All Fields]) OR "roc analysis"[All Fields]) OR "roc and"[All Fields]) OR "roc area"[All Fields]) OR "roc auc"[All Fields]) OR "roc characteristics"[All Fields]) OR "roc curve"[All Fields]) OR "roc curve method"[All Fields]) OR "roc curves"[All Fields]) OR "roc estimated"[All Fields] OR "roc evaluation"[All Fields] OR "likelihood ratio"[All Fields])

**RCT terms**

Clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials[mh] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT (animals[mh] AND humans[mh]))

Figure 1. Search strategy

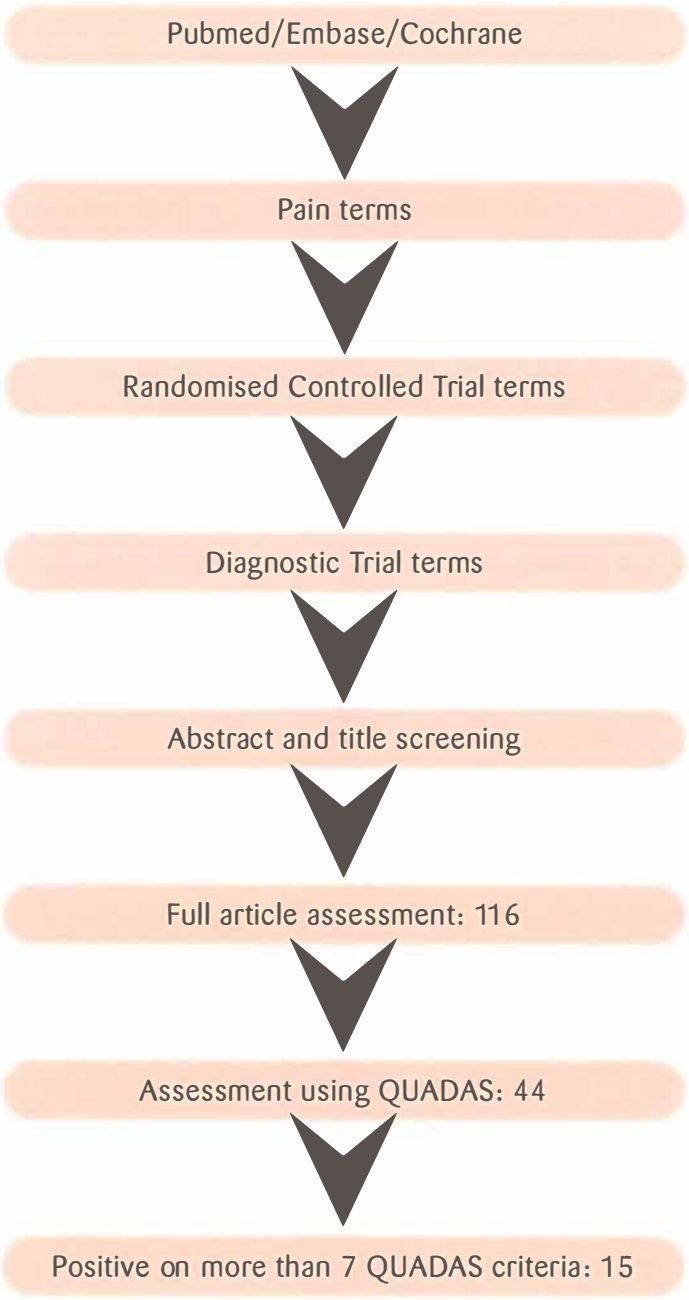


Table 2. Quality Assessment of Diagnostic Accuracy Studies list (QUADAS), used in this study to assess internal validity (Whiting et al., 2004)

| | |
|---|---|
| 1. | Was the spectrum of patients representative of the patients who will receive the test in practice? |
| 2. | Were selection criteria clearly described? |
| 3. | Is the reference standard likely to correctly classify the target condition? |
| 4. | Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests? |
| 5. | Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis? |
| 6. | Did patients receive the same reference standard regardless of the index test result? |
| 7. | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard) |
| 8. | Was the execution of the index test described in sufficient detail to permit replication of the test? |
| 9. | Was the execution of the reference standard described in sufficient detail to permit its replication? |
| 10. | Were the index test results interpreted without knowledge of the results of the reference standard? |
| 11. | Were the reference standard results interpreted without knowledge of the results of the index test? |
| 12. | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |
| 13. | Were uninterpretable / intermediate test results reported |
| 14. | Were withdrawals from the study explained? |

## Results

### Search results

The search of the databases identified 1074 articles. After screening the titles and abstracts, 116 potentially relevant references were retrieved in full. After reading these full versions, 72 articles did not meet the inclusion criteria concerning purpose and design as mentioned earlier. Eventually, 44 articles were assessed using the QUADAS, of which 15 studies were considered to be of adequate quality for further assessment, i.e. scored "yes" on the QUADAS in more than 7 of the 14 items. The manual cross-reference search of eligible studies was performed did not yield any other relevant studies. Inter-observer agreement was calculated for agreement in inclusion of appropriate studies. A consensus discussion was needed 7 times, and resolvement of disagreement by a third party was unnecessary. Kappa was: 0.81 (95% CI: 0.64-0.99).

### Description of the studies

Of the 15 studies included, the design and outcome details are listed in table 3. The results of the qualitative appraisal using the QUADAS criteria of all studies are listed in table 4. Of all studies, eight investigated the diagnostic value of magnetic resonance angiography (MRA) for vascular compression in trigeminal neuralgia (TN). Patients that were clinically suspect for trigeminal neuralgia and were referred for (surgical) treatment underwent MRA. Subsequently, the surgery was performed (i.e., decompression was performed in case of compression of the nerve) and the findings were compared with the findings during MRA (Anderson et al., 2006; Benes et al., 2005; Boecher-Schwartz et al., 1998; Fukuda et al., 2006; Korogi et al., 1995; Meaney et al., 1995; Patel et al., 2003; Vörös et al., 2001). Of these studies, only Fukuda and co-workers used a two dimensional MRA technique (Fukuda et al., 2006); the other studies used three dimensional MRA. Also, Fukuda included hemifacial spasm patients. In table 4 an overview of the MRA studies is provided. All studies were conducted in hospitals. Most patients were referred for decompression surgery (Anderson et al., 2006; Benes et al., 2005; Boecher-Schwartz et al., 1998; Fukuda et al., 2006; Korogi et al., 1995; Meaney et al., 1995; Patel et al., 2003). Eligible patients underwent the imaging procedure, which was interpreted by a neuroradiologist. The surgery was performed by a neurosurgeon. In five studies, the department of neuroradiology was situated in a university hospital (Anderson et al., 2006, Boecher-Schwartz et al., 1998; Korogi et al., 1995; Meaney et al., 1995; Vörös et al., 2001) for the department of neurosurgery this was the case in four studies (Anderson et al., 2006, Boecher-Schwartz et al., 1998; Korogi et al., 1995; Vörös et al., 2001). Patients with TN or patients with TN referred for surgery were included (Anderson et al., 2006; Benes et al., 2005; Boecher-Schwartz et al., 1998; Fukuda et al., 2006; Korogi et al., 1995; Meaney et al., 1995; Patel et al., 2003; Vörös et al., 2001). When interpreting the MRA's, the neuroradiologist was blinded in four studies (i.e., with regard to the clinical information (Korogi et al., 1995; Patel et al., 2003) or with regard to which side was affected (Anderson et al., 2006; Benes et al., 2005), while in the other four studies no information about the blinding of the neuroradiologist was provided Boecher-Schwartz et al., 1998;

Fukuda et al., 2006; Meaney et al., 1995; Vörös et al., 2001). The neurosurgeon was aware of the MRA findings in four cases (Anderson et al., 2006; Fukuda et al., 2006; Meaney et al., 1995; Patel et al., 2003), while the other studies (Benes et al., 2005; Boecher-Schwartz et al., 1998; Korogi et al., 1995; Vörös et al., 2001) did not provide information about the blinding of the neurosurgeon. In the all investigations, it remained unclear how long after the MRA assessment surgery took place. In none of these studies, clear inclusion criteria were reported.

Three studies reported the diagnostic value of magnetic resonance imaging (MRI) in temporomandibular joint (TMJ) arthralgia (Murakami et al., 1996; Ohlman et al., 2006; Schaefer et al., 2001). In one of these studies, the validity of different pain pressure thresholds was also studied (Schaefer et al., 2001) Details are listed in table 4. The studies were all performed in a university setting. Patients seeking treatment for their TMD were first diagnosed using the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) (Ohlman et al., 2006) or diagnosed with closed lock (Murakami et al., 1996) and thereafter MRI was performed and blindly interpreted. In Schaefer's study, patients with unilateral or bilateral TMJ disc displacement with reduction, according to the RDC/TMD, and meeting the criteria for arthralgia, were included. MRI's were studied for the presence of disc displacement with or without reduction, osteaoarthritis and joint effusion. Time between reference test and index test was appropriate (i.e. short enough to prevent the targeted disease from changing clinical features) in this study (Schaefer et al., 2001).

Konan and co-workers studied a bite test for identifying whether pain in the TMJ region is of muscular or articular origin (Konan et al., 2003). Patients with temporomandibular disorders were included and patients had to bite on a wedge on the painful as well as on the non-painful side. When this test causes temporomandibular pain on the ipsilateral side, the pain was interpreted as being of muscular origin whereas contralateral TMJ pain would suggest a joint problem. The proposed origin of pain was blindly compared with possible articular changes on MRI's, i.e. joint space narrowing, retrusion of the mandibular condyle and bony signs of joint degeneration (Konan et al., 2003).

Zuniga and co-workers performed neurophysiological tests in patients with either alveolar nerve or infraoribtal nerve deficits (Zuniga et al., 1998). A combination of different neurophysiologic test findings was related to the surgical findings. Zuniga's study included patients from three academic and two peripheral oral and maxilofacial surgery practices. Patients with a neurosensory complaint in the distribution of either inferior alveolar nerve or lingual nerve injuries were included. Based on an algorithm using a set of sensory tests for the inferior alveolar nerve or the lingual nerve, sensory impairment was scored being: normal, mild, moderate, severe or complete. The surgical findings were categorized as: normal/intact, compressed/intact, neuroma-in-continuity, partial transection and complete transection. Test and surgical findings were compared; no information was given about the blinding procedure.

Cisneros-Cabello and colleague studied the diagnostic value of pain complaints and symptoms and pulpal tests in patients with pulpal problems, i.e. patients in need for endodontic treatment (Cisneros-Cabello and Segura-Egea, 2005). In a university setting, they included patients in need of endodontic treatment because of pulpal pathosis. Pain was assessed based on the history and after several thermal and provocative tests. Hereafter, pulps were removed and prepared for histology. Using developed criteria (Selzer and Bender, 1990) the investigators classified patients histopathologically in the following diagnostic categories: intact noninflamed pulp, atrophic pulp, acute pulpitis, transitional stage of pulpitis, chronic pulpitis, total pulp necrosis, and acute pulpitis superimposed on a chronic pulpitis. The authors distinguished treatable (reversible) pulp status from untreatable pulp (irreversible) status (pulpitis cases) and compared pain complaints with the histopathological diagnosis. The specificity and sensitivity of the different complaints and tests are listed in table 5. No information concerning blinding procedures was provided. Whether the time between clinical diagnosis and histopathological diagnosis was sufficient, as well as the selection criteria for eligible patients remained unclear.

To study the validity of intra-articular tempromandibular joint pain, patients clinically diagnosed with articular pain received both placebo and anaesthesia in a cross-over double blind fashion (Tjakkes et al., 2007) in the oral and maxilofacial surgery department of a university hospital. Patients with preauricular pain, clinically diagnosed using the RDC/TMD with articular TMJ pain, were included. Physician and patients were blinded to the injected solutions. Pain and maximal mouth opening (MMO) were measured before and after anesthesia and placebo injections and differences were analyzed. Pain was significantly more increased after anesthesia compared to placebo injection. No differences were found between the two substances concerning MMO.

## Discussion

This study aimed at identifying and appraising the evidence-base for diagnostic tests for orofacial pain. For the identification of articles on the subject, terms were collected for pain in the orofacial region. Furthermore, a search string developed for systematic reviews for diagnostic accuracy was used (Devillé et al., 2002). To include diagnostic studies performed in a randomized clinical trial, a search string for RCT's was used additionally (Glanville et al., 2002). Although our initial search resulted in numerous studies, only minority remained, when methodological criteria were applied. After applying criteria for quality assessment, only 15 studies fulfilled more than 7 of 14 QUADAS criteria. The QUADAS criteria were developed to enhance systematic quality assessment for the use in systematic reviews of diagnostic accuracy studies (Whiting et al., 2003). When studies are appraised in reviews, not only should the test performance (which includes a test's properties like sensitivity, specificity, positive and negative predicative values) be described, but also the methodological quality of these studies. Items included in the QUADAS are the result of a Delphi procedure. The 14 items relate to methodological facets of a study. From a list with potentially relevant items, eventually 14 items remained for inclusion in the list. This list does not corporate a quality score. As this review includes different types of orofacial pain and different types of diagnostic studies, it seemed unfair to introduce a quality score that is applied to all the different types of studies. However, to include studies which are potentially of good quality, we decided that at least 8 items (more than half) should be answered affirmatively. This cut-off point has also been used by other authors in their reviews (Graaf de et al., 2006; Seghal et al., 2007). As a consequence, studies that could have been of good quality but without an adequate report of these different aspects of quality, have not been included in our study.

Interestingly, the majority of the included studies concerned MRA findings versus clinical findings in trigeminal neuralgia. This may be due to the fact that the diagnosis of trigeminal neuralgia is clearly described by the current classification systems (Merskey and Bogduk, 1994; Olesen, 2004). Moreover, the incidence of this disease makes clinical trials easier to conduct than trials in rare conditions. The etiology is often sought in compression of the nervus trigeminus. This may relatively easy be demonstrated by neurosurgery. Presurgical images may be compared by surgical findings, which serve as the gold standard. The sensitivities and specificities of the included trigeminal neuralgia studies are mostly moderate to high, when studied in different study population sizes. This seems to justify the use of MRA in patients that are clinically diagnosed with trigeminal neuralgia for the detection of vascular compression. Thereafter, surgery aiming at decompression may alleviate the symptoms. In addition, MRA in patients with trigeminal neuralgia caused due to other causes than compression, e.g. a tumor or multiple sclerosis, can provide the clinician with relevant diagnostic information.

Another diagnostic test that has been reported was MRI in diagnosing temporomandibular disorders (Murakami et al., 1996; Ohlman et al., 2006; Schaefer et al., 2001). All studies specifically focused on the use of MRI in diagnosing TMJ arthralgia.

Table 3. Study design details of included studies

| | Patient group | Test | contrast |
|---|---|---|---|
| Korogi et al. 1995 | TN | 3D TOF MRA | gadolinium |
| Meaney et al. 1995 | TN | MRTA FISP 3D | gadolinium |
| Boecher-Schwartz at al. 1998 | TN | MRA 3D MPFFES | gadolinium |
| Vörös et al. 2001 | TN | 3D TOF MRA | gadolinium |
| Fukuda et al. 2003 | TN | MRTA (2D) | none |
| Patel et al. 2003 | TN | MRA 3D FFE | gadolinium |
| Benes et al. 2005 | TN | 3D FSPGR | gadolinium |
| Anderson. 2006 | TN | 3D TOF MRA | gadolinium |
| Murakami et al. 1996 | TMJ arthralgia | MRI | |
| Schaefer et al. 2001 | TMJ arthralgia | MRI | |
| Ohlmann et al. 2006 | TMJ arthralgia | MRI | |
| Tjakkes et al. 2006 | TMJ pain | local anesthesia | |
| Konan et al. 2003 (JSN) (MR) (JD) | TMD | CT | |
| Cisneros-Cabello et al. 2005 | tooth pain | pain complaints/ pulpal tests | |
| Zuniga et al. 1998 (IAN) | nerve injury | neurosensory tests | |

| | |
|---|---|
| Sens: | sensitivity |
| Spec: | specificity |
| N/A: | not applicable |
| TN: | trigeminus neuralgia |
| MRA: | magnetic resonance angiography |
| MRTA: | magnetic resonance tomographic angiography |
| 3D FFE: | three-dimensional fast field-echo |
| 3D MPFFES: | three-dimensional magnetisation prepared fast field-echo sequence |
| FISP 3D: | three-dimensional fast imaging with steady-state precession |
| 3D TOF MRA: | three-dimensional time-of-flight magnetic resonance angiography |
| MRTA: | magnetic resonance tomographic angiography |

| reference test | N | N control | sens | spec |
|---|---|---|---|---|
| surgical findings | 16 | - | 75 | 72 |
| surgical findings | 50 | - | 96 | 100 |
| surgical findings | 27 | - | 88.5 | 50 |
| surgical findings | 172 | - | 97.6 | 92.5 |
| surgical findings | 21 | - | 67 | 90.5 |
| surgical findings | 92 | - | 90.5 | 100 |
| surgical findings | 21 | - | 52.3 | 50 |
| surgical findings | 48 | - | 76 | 75 |
| clinical (closed lock) | 19 | - | 53 | N/A |
| clinical (RDC/TMD) | 14 | 16 | 85 | 28 |
| clinical (RDC/TMD) | 68 | 214 | 32 | 72 |
| clinical (RDC/TMD) | 19 | * | N/A | N/A |
| bite test | 32 | - | 88.9 | 58.1 |
| | | | 88.9 | 64.5 |
| | | | 100.0 | 38.7 |
| histopathology | 250 | - | see table 4 | |
| surgical findings | 130 | - | 60.0 | 77.8 |
| | | | 100.0 | 95.4 |

| | |
|---|---|
| 3D FSPGR: | three-dimensional fast spoiled gradient-echo |
| MRI: | magnetic resonance imaging |
| TMD: | temporomandibular disorders |
| RDC/TMD: | Research Diagnostic Criteria for Temporomandibular Disorders |
| CT: | computed tomography |
| * | cross-over study design |
| IAN: | inferior alveolar nerve |
| LN: | lingual nerve |
| JSN: | joint space narrowing |
| MR: | mandibular retrusion |
| JD: | signs of joint degeneration |

Table 4. Results of the qualitative appraisal of all studies using the QUADAS

| QUADAS Question | Murakami et al., 1996 | Fukuda et al., 2003 | Schaefer et al., 2001 | Konan et al., 2003 | Benes et al., 2005 | Cisneros-Babello et al., 2005 | Ohlmann et al., 2006 | Zuniga et al., 1998 | Korogi et al., 1995 | Boecher Schwartz et al., 1995 | Anderson et al., 2006 | Meaney et al., 1995 | Patel et al., 2003 | Vörös et al., 2001 | Tjakkes et al., 2007 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 2 | N | N | Y | Y | N | N | Y | Y | N | N | Y | N | N | ? | Y |
| 3 | Y | Y | Y | ? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 4 | ? | ? | Y | N | ? | ? | ? | ? | ? | ? | ? | ? | ? | ? | ? |
| 5 | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y |
| 6 | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y |
| 7 | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | Y |
| 8 | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 9 | Y | Y | Y | Y | Y | Y | Y | Y | ? | Y | Y | Y | Y | Y | Y |
| 10 | ? | ? | Y | Y | Y | Y | Y | Y | ? | ? | ? | ? | Y | ? | Y |
| 11 | Y | N | Y | Y | ? | ? | Y | Y | Y | N | N | N | N | ? | Y |
| 12 | Y | Y | Y | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y |
| 13 | N | ? | ? | ? | ? | ? | N | N | N | Y | Y | Y | Y | Y | Y |
| 14 | N | N | ? | ? | ? | ? | Y | N | N | Y | Y | Y | ? | Y | Y |

Y: answer yes N: answer no ?: not clear

Table 5. Specificity and sensitivity of different patient complaints in the diagnosis of untreatable pulpal status. (adapted from Cisneros-Cabello et al. 2005)

| | Specificity (%) | Sensitivity (%) |
|---|---|---|
| Previous pain | 95.2 | 38.9 |
| Spontanuous pain | 95.2 | 61.1 |
| Pain on cold stimuli | 28.6 | 100.0 |
| Pain on heat stimuli | 97.6 | 22.2 |
| Pain on sweet stimuli | 95.2 | 22.2 |
| Pain on chewing | 73.8 | 27.8 |
| Pain on lying down | 90.5 | 27.8 |
| Pain on palpation | 97.6 | 5.6 |

Ohlmann (Ohlman et al., 2006) studied whether MRI findings (disc displacement, osteoarthritis, and joint effusion) could predict TMJ pain, diagnosed using the RCD/TMD. The authors found no relationship between the MRI diagnosis and TMJ arthralgia. However, apart from the clinical and MRI findings, authors used different questionnaires to assess somatisation, jaw disability, and psychological health. Outcomes of this assessment were also included in the performed regression analysis. However, inserting more variables in a regression analysis influences which and how many predictors are eventually found. Taking into account the low to moderate sensitivities and specificities, it is disputable whether the costs of an MRI as well as the waiting list justify the use of an MRI in diagnosing arthralgia.

The use of the Krogh-Poulsen test, consisting of biting on a wedge on one side, was studied by Konan and co-workers (Konan et al., 2003). When joint pain was detected using the test, the authors mentioned that radiographic CT showed joint involvement in all of these patients. When the test suggested a muscular origin of the pain, 70% of the CT scans did not show any abnormality. The authors concluded that these results justify the use of this test in determining the origin of temporomandibular pain, which is debatable as muscular pain may be accompanied by a damaged but non-painful joint, and a painful joint may show no lesions on the CT. Moreover, pain cannot be seen on a CT. Therefore, the clinical validity of the authors' conclusions are dubious and the diagnostic value of this test is uncertain.

To study the accuracy of neurosensory testing (NST) in diagnosing trigeminal nerve injuries, neurosensory findings in patients with either inferior alveolar or lingual nerve injuries were compared with surgical findings (Zuniga et al., 1998). Although the execution of the study seemed sound, no information could be retrieved concerning the time between NST and surgical findings, which could have hampered the results. Neurosensory signs may change over time. For accurate findings and subsequent interpretation, to prevent change of neurosensory signs, the time between NST and surgery should therefore be minimized. The NST can be of help in staging the neurological deficit, but is not suitable for purely diagnostic use.

In tooth pain, diagnostic tests are used in order to assess the pulpal condition. Cisneros-Cabello and colleague (Cisneros-Cabello and Segura-Egea, 2005) studied the relationship between pain complaints, pulpal tests, and the histopathological diagnosis. Thereafter the sensitivity and specificity as well as reliability of the pain complaints in the untreatable (i.e. irreversible) pulp status were calculated. The authors defined reliability as the percentage of true results (in addition to true positives and true negatives). To our opinion, in this case the reliability should refer to the consistency of test result from a test, i.e. test-retest reliability. To distinguish between reversible and irreversible pulp status seems reasonable, as it relates to the indication of (invasive) treatment. The authors discuss a few significant correlations between pulp status and pain complaints and their corresponding sensitivity and specificity. However, no single pain complaint showed both satisfactory sensitivity and specificity. Although omitted, this offered the authors

an opportunity to combine different complaints as diagnostic tests, in order to suggest practical guidelines.

To study the effect of injection of an anesthetic solution in the temporomandibular joint as a diagnostic test, Tjakkes and colleagues (Tjakkes et al., 2007) studied the effect on pain and maximal mouth opening ability in a cross-over placebo controlled trial. No differences were found with respect to mouth opening between the two solutions. The authors did find a difference in pain relieve between anesthesia and placebo. However, on average the pain was not completely reduced after anesthesia. Although clinical examination lead to the conclusion that the pain was of articular origin, nearby painful (e.g. muscular) structures may have also been responsible for the pain felt in the temporomandibular joint region. This may have had an effect of the (lack of) pain diminishing effect of the anesthestic solution in some cases. Therefore the results of diagnostic anesthesia should be interpreted carefully before any (irreversible) intervention is considered.

In most of the studies, tests are performed in patients who have been diagnosed or included based on clinical criteria from existing classification systems; patients with clear symptoms are used. This will have an effect on the diagnostic performance of the test. Test outcomes may be less obvious or harder to interpret in patients in other (i.e. less severe) stages of the disease. This affects the generalizability of the study outcomes and also explains the lack of studies concerning less obvious orofacial pains.

Our results indicate that, when applying a tool which assesses the quality of diagnostic research, only a minority of the studies are of sufficient methodological quality. This is remarkable, as orofacial pain and accompanying diagnostic tests are common in dental and medical practice. Orofacial pains that are well defined and can be easily diagnosed based on clinical examination have been studied well and are of sufficient quality. Less well defined pains, which merely refer to chronic idiopathic orofacial pains, do not seem to be captured easily within a (single) diagnostic test. In chronic orofacial pain, which can hardly be differentiated using standard assessment tools, there is still need for new diagnostic tools that differentiate between different pain categories, which may provide directions for subsequent treatment.

In theory, the process leading to a diagnosis seems relatively easy, which in a majority of (acute) pain problems may also be the case. In complex cases, where the initial diagnostic process (including proper history taking and clinical examination) has not yet led to a diagnosis, there is an urgent need for more diagnostic information. This hides the danger of overestimating the information obtained from the performed test. Although attempts have been made to enhance the diagnostic process and to expand the diagnostic possibilities, a larger diagnostic armamentarium is warranted in order to be able to differentiate between different diagnostic subgroups in chronic idiopathic orofacial pain patients. Once this differentiation can be validly and reliably made, this may enhance the subsequent treatment.

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# The effect of intra-articular injection of ultracain in the temporomandibular joint in patients with pre-auricular pain. A randomized prospective double blind placebo controlled crossover study

*This chapter is based on: The effect of intra-articular injection of ultracain in the temporomandibular joint in patients with pre-auricular pain. A randomized prospective double blind placebo controlled crossover study. Tjakkes GH, TenVergert EM, de Bont LGM, Stegenga B, published in The Clinical Journal of Pain, 2007: 23:233-236.*

# 3.1

## Abstract

**Aims:** To evaluate the distinguishing ability of intra-articular anaesthesia from placebo in orofacial pain patients with pain located in the temporomandibular joint (TMJ) region, aiming at a validation of intra-articular anaesthesia injection as a diagnostic test of pain in the TMJ region.

**Materials and methods:** A randomized prospective double blind placebo-controlled crossover study was conducted among 19 patients (18 females, 1 male) with pain in the TMJ region. The short-term effects of intra-articular ultracain and saline injections on pain and maximum mouth opening (MMO) were measured and analysed.

**Results:** Compared to placebo injections, a statistically significant difference in pain scores was found after intra-articular injection of a local anaesthetic as far as Visual Analogue Scale scores were concerned. The MMO scores did however not differ between the two groups.

**Discussion:** TMJ injection with local anaesthesia leads to decrease of pain in patients with preauricular pain. In order to establish the source of pain, injection of a local anaesthetic in the TMJ may be used as a diagnostic tool. However, the results of diagnostic injections should still be interpreted cautiously.

## Introduction

Temporomandibular disorders (TMD) comprise disorders of the temporomandibular joint (TMJ) and its associated muscles. Currently, pain conditions in general and TMD in particular are classified according to a bi-axial system. Axis I includes physical conditions (the 'disease'), while axis II involves the pain-related disability and psychological status (the 'illness'). According to the research diagnostic criteria (RDC), axis I classification consists of three subgroups, i.e., muscle disorders, disc displacements and a group labelled "Arthralgia, arthritis and arthrosis". (Dworkin and Le Resche, 1992) These subgroups are not mutually exclusive, but the specific disorders within the subgroups are. It has been suggested to classify the specific TMD in accordance with the classification of other synovial joints, based on intra-articular pathologic processes. (Stegenga, 1991, 1996) The articular TMD consist of disorders of the joint itself (e.g. osteoarthrosis, internal derangement, intra-articular fractures, infections, tumours and inflammatory disorders). The non-articular TMD comprise disorders of the muscles associated with the TMJ, among other disorders. This classification also recognizes that the TMJ as well as its associated muscles may be involved in generalized disorders, such as rheumatoid arthritis, fibromyalgia, or polymyalgia rheumatica.

Pain perceived in the temporomandibular joint area may originate from the joint proper as well as from other nearby and distant structures. A thorough history, complete physical and radiographic examination usually lead to a diagnosis, although sometimes further diagnostic tests are needed. Okeson has defined primary pain as pain that emanates from a structure that hurts, whereas in secondary pain the site of pain differs from the true location of its source. (Okeson, 1995) Additional clinical diagnostic tests (based on the response to provocation) and analgesic blockade with local anaesthesia could assist in establishing a diagnosis.

A positive response to a local anaesthetic (i.e. diminishing the pain) is frequently used as a justification for further (nonsurgical and surgical) therapy. It may also be used as an inclusion criterion in (experimental) studies. Despite these – sometimes far-reaching – consequences, the validity of such a diagnostic test has not been formally established. The aim of this study was to evaluate the distinguishing ability of intra-articular anaesthesia from placebo in orofacial pain patients with pain located in the TMJ region. The hypothesis whether intra-articular local anesthesia (ultracain) relieves pain more and improves the maximum mouth opening (MMO) to a greater extent than placebo in patients with pre auricular pain, was tested.

## Materials and Methods

### Patients

Patients meeting the criteria of Axis 1 of the type III group of the research diagnostic criteria based on clinical assessment were subjects of this study. This group of diagnoses consists of "arthralgia, osteoarthritis and osteoarthrosis" of the TMJ. (For details see Dworkin and LeResche, 1992). Consecutive patients with painful types of above mentioned TMD referred to the Orofacial Pain section of the Department of Oral and Maxillofacial Surgery at the University Medical Center Groningen (UMCG) were asked to participate in the study. Additional inclusion criteria were: age between 16-65 years, presence of subjective mandibular movement restriction and/or function impairment. Standard clinical examination, existing of assessing TMJ pain and measurement of function impairment, patients' subjective complaints were confirmed, in order to be able to allocate suitable patients meeting the above mentioned criteria into the study population. Patients with predominantly myogenic pain dominating the pain complaints, odontogenous causes of pain such as pericoronitis, or tumours in the orofacial area were excluded. To screen the patient's psychological status in a hospital setting the Hospital Anxiety and Depression Schedule (HADS) (Zigmond and Snaith, 1983) measuring anxiety (HADS-A) and depression (HADS-D) was used. Eligible patients gave informed consent after receiving oral explanation and written information about the study design and the specific requirements related to participation of the study. The patients did not receive monetary compensation. This study was approved by the Medical Ethical Committee of the UMCG.

### Study design

The present study was designed as a prospective randomized double-blind placebo-controlled crossover trial. The (most) painful TMJ of each patient was injected twice. To reduce confounding of injections with the order in which they were administered, the injections were allocated in a randomized fashion. The washout phase between injections with articaine hydrochloride with 1:200,000 epinephrine (Ultracain D-S; Aventis®, The Netherlands) and injections with sterile normal saline or vice versa was two weeks. The sequence of injection was randomized. The randomization was performed by computer using the randomization function of StatsDirect™. The pharmacy of the UMCG prepared the injection fluids, which were supplied in identical ampules in a coded box. Thus, the patient, the clinician who performed the injection, and the clinician who performed the assessments were all unaware of which solution was injected.

In order to prevent possible bias from anaesthetic skin sensation following the injection with ultracain, all patients were supplied with topical anaesthesia of the skin in the preauricular area (lidocain 25 mg / prilocain 25 mg, EMLA®, AstraZeneca, USA) for at least 45 minutes. The past and current TMJ pain intensity were assessed (see below). In addition, the patients were requested to answer several questionnaires (see below). The maximum assisted interincisal distance and the level of pain were measured during the clinical examination, immediately preceding (i.e., after 45 minutes of topical anaesthetic application) and following the injection.

After removal of the EMLA topical anaesthesia, the skin overlying the joint area was cleaned and disinfected with a 70% ethanol solution. Subsequently, the upper compartment and capsule of the joint were injected with either 0.5 ml ultracain or 0.5 ml saline. During each visit, the patient was carefully monitored with respect to possible side effects. Also, in case of any problems between or after the two visits, patients could contact an independent oral and maxillofacial surgeon. After enrolment of all patients, the blinding code was broken and data were analysed.

**Pain assessments**

TMJ pain intensity was recorded at arrival, after initial MMO measurement, after 45 minutes with topical anaesthesia, after subsequent MMO measurement, 2 minutes after the injection, and after the final MMO measurement (5 minutes after injection). A Visual Analogue Scale (VAS) (Price et al., 1983), i.e., a 100 mm scale with endpoints designated as 'no pain' and 'worst pain imaginable' was used for pain intensity assessment.

**Assessment of movement restriction and function impairment**

The MMO was measured at three occasions, i.e. during the clinical examination, after 45 minutes of topical anaesthesia immediately before injection, and 5 minutes following the injection. The patients were requested to open as wide as possible, after which the distance between the upper and lower lateral incisors was measured with a millimetre ruler. At each occasion, the MMO was recorded three times. This measurement has been found to be highly reliable (intraclass correlation = 0.96) (Dworkin and Le Resche, 1992)

The patients' mandibular (dys)function was assessed with the Mandibular Function Impairment Questionnaire (MFIQ) (Stegenga et al., 1993b). A Function Impairment Rating Score (range 0-5) of mandibular function was calculated, scores 0 and 1 representing a low, scores 2 and 3 a moderate, and scores 4 and 5 a severe level of function impairment.

**Statistical analysis**

Data were analysed using SPSS 12 (SPSS Inc, USA). To check normality of differences in VAS and MMO scores before and after ultracain and placebo injection, the Kolmogorov-Smirnov test was performed. After proof of normality, t-tests for paired samples were performed to test the differences between VAS scores and MMO scores after ultracain and after placebo injection. HADS and MFIQ scores were presented descriptively.

## Results

In total 20 patients were enrolled in this study (19 females and 1 male). Their age ranged from 18 to 62 years, with a mean age of 32.5 years (SD=12.0 years). One female patient decided to withdraw from the study after the first (in her case placebo) injection for personal reasons.

The mean HADS-A score and the mean HADS-D score was, respectively, 4.6 (SD=3.6) and 5.1 (SD=2.9) on a 0-14 point scale. Both scores were below the range of values in the general population (average score of < 7) which indicates no signs of anxiety or depression in the included patients. The mean function impairment score at the first visit was 3.5 (SD=1.3) on a 1-5 point scale (i.e., moderate-severe function impairment).

After the ultracain injection VAS scores in the ultracain group decreased from 65.7 (SD=22.9) to 52.9 (SD=30.9). The VAS scores after injection with placebo increased from 57.8 (SD= 21.7) to 62.3 (SD=26.7). Consequently, the mean VAS difference after ultracain injection was -12.8 (SD 23.5) and the mean VAS difference after placebo injection was 4.5 (SD 15.0). This difference between VAS scores before and after ultracain and placebo injections was statistically significant (p= 0.014).

The mean difference in MMO scores before and after ultracain injection and placebo injection was, respectively, 2.0 (SD=2.9) and 0.4 (SD=2.9) compared to the situation before injection. This difference between the MMO score differences of the ultracain and placebo group was not statistically significant (p= 0.103)

## Discussion

Our results show that there is a statistical significant difference in pain scores after injection with a local anaesthetic compared to the pain scores following a placebo injection. The effect of the injection of a local anesthetic may therefore be used as a diagnostic tool in the assessment of TMD in order to establish the source of pain.

For treatment planning, establishing the source of pain in the TMJ region may be vital. In patients presenting with preauricular pain, it is important to distinguish articular from non-articular sources of pain. Anaesthesia of the joint by injecting a local anaesthetic into the intra-articular space is frequently used as a diagnostic tool, but has never been validated for that purpose. Effects of intra-articular local anaesthesia injections have been studied in other joints. A systematic review of studies about pain relief following intra-articular local anaesthesia injection compared to no or placebo treatment after arthroscopic knee surgery showed that 8 out of 20 studies reported no improved pain relief after local anaesthesia injection (Møiniche et al., 1999).

In a recent opinion article, the use of intra-articular TMJ anaesthesia injections for the use in diagnosing and treating TMJ and myofascial pain was promoted, (DuPont, 2004) using a short-acting plain anaesthesia (e.g. 2% lidocaine or 3% carbocaine). If significant pain reduction after 10 minutes followed, the TMJ would probably be the source of pain. This seems to be an useful method of establishing a diagnosis, however, no evidence for the offered statements was offered. Danzig et al. have found significant pain decrease after intra-articular injection of an anaesthetic solution in the TMJ of patients with persistent TMD. (Danzig et al., 1992) No placebo controlled design was used however, making the attribution of pain relief solely to the anaesthetic solution questionable.

In order to prevent care providers from drawing erroneous conclusions after anaesthetic injections, we studied this diagnostic tool in a randomized, double-blind placebo-controlled manner. In other designs, articular injections, of other substances e.g. opioids, have been evaluated, with or without a combination of a local aesthetic. We did not study the long term effect of the injections as it was validated for the purpose of an aid in the diagnosis of orofacial pain. Normally this diagnostic test will take place in a clinical setting in which the clinician relies on the immediate (early) response of the patient. Long-term effects were only taken into account in calculating the period-effect which appeared to be negligible. Therefore, long-term effects for this purpose were considered as being irrelevant.

The reduction in VAS scores after anaesthesia injection was found to be relative. This may be due to technical factors e.g. varying anatomical structures, different concentration and volumes of anaesthetic used, or psychological effects. Another reason that may have lead to incomplete pain reduction is that for analysis of the value of a diagnostic test, one needs to have a golden standard. We included our patients using the diagnostic criteria, as mentioned earlier using a standard clinical examination as well as the MFIQ,

to ensure that patients with mainly articular pain would participate in our study. This means that the inclusion took place without the aid of a golden standard test, as it does not exist for these disorders. Therefore, included patients could have had coexisting pain problems, e.g. myofascial pain contributed to the TMJ pain and therefore the effect of the injections. According to the HADS, our patients showed no signs of psychological distress and thus the perceived pain may be considered as being of merely somatic origin.

Furthermore, incomplete pain relief may also be due to incomplete anaesthesia of the responsible nerve endings. By injecting in the TMJ, some parts of the superior branch of the auriculotemporal nerve may be left unaffected resulting in inadequate anaesthetic effect and may lead occasionally to incorrect conclusions.

In our study we found no significant difference in maximum mouth opening between the above mentioned groups. This may be due to the fact that at every MMO measurement, the anatomical limit of mouth opening was achieved and would, therefore, not be influences by the type of injected solution.

We have chosen to compare the effects of ultracain with the effects of saline, a placebo, in order to be able to judge the effect of the ultracain solely on the based on the anaesthetic effect. A positive response to placebo however, does not imply that the patient is malingering, as a placebo response is obtained in approximately 33% of all subjects (Gross, 1991), although the effect of placebo has not shown to be clinically relevant (Hróbjartsson and Gøtzsche, 2006) The suggestion that a pain relieving treatment has been given may be sufficient to provide pain reduction. (Fields and Price, 2006) However, in the design used in our study patients were informed that they would receive both placebo and anaesthesia, indeed in a double blind manner, so this may have led to a reduction of the pain diminishing effect of the placebo. Immediate short-time results after diagnostic anaesthesia should not be misinterpreted. As stated above, a pain diminishing effect could be due to placebo response. Patients may also be eager to response positive in their eagerness to help diagnose their problem or to get treatment.

In summary, our results suggest that TMJ pain perception after injection of an anaesthetic agent does differ from the perception after placebo injection. As an aid in the diagnostic process, intra-articular injections may be used, but one should still be cautious in interpreting the results. Therefore, we recommend verifying the outcome of diagnostic injections at least once before coming to conclusions.

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# Classification of chronic orofacial pain using an intravenous diagnostic test

*This chapter is based on: Classification of chronic orofacial pain using an intravenous diagnostic test. Tjakkes GH, De Bont LG, Van Wijhe M, Stegenga B. published in The Journal of Oral Rehabilitation. 2009; 36: 469-475.*

# 3.2

## Abstract

**Aims:** The aim of this study was to evaluate the results of a preliminary intravenous diagnostic test.

**Patients:** Patients with chronic orofacial pain conditions that could not be unambiguously diagnosed.

**Design:** A retrospective evaluation of series of conducted pharmacodiagnostic tests, consisting of the consecutive intravenous administration of drugs.
Outcome measures: Visual Analogue Scale scores were retrieved from all patients, based on which they were classified into different responder groups.

**Results:** In total, 46 pain profiles were analysed. Of these, 16 patients (35%) could be classified into one or more pain categories, while 30 patients (65%) could not be classified into any pain category. The pain duration or medication use did not influence the classification.

**Conclusion:** Based on the results of this retrospective study, it seems that classification into subgroups is possible after intravenous testing in a minority of clinically unclassifiable patients. In patients where there is a substantial need for additional diagnostic information, these results may be of value. Recommendations are made for further research, which should include validation in patients with known pain mechanisms.

## Introduction

Orofacial pain, referring to pain experienced in the mouth and facial area, is very common in medical and dental practice (Macfarlane et al., 2002). A median prevalence of 13% has been described based on epidemiological studies (Macfarlane et al., 2001). Facial pains include odontogenic pains, painful diseases of the oral mucosa and salivary glands, temporomandibular disorders, and neurological (e.g. neuralgia) and vascular pains (e.g. temporal arteritis, migraine). The diagnosis of these orofacial pains is usually straightforward, the majority being acute or transient in nature. Pain associated with temporomandibular disorders and neurovascular mechanisms may, however, be more persistent (Sessle 2000; Israel et al., 2003).

Chronic orofacial pain conditions are often difficult to diagnose and manage. Pains that cannot be readily diagnosed are frequently referred to as 'atypical', implying that typical facial pains have been excluded (Israel et al., 2003). In the classification of the International Headache Society, a subgroup "persistent idiopathic facial pain" exists, which includes atypical facial pain and atypical odontalgia (Headache Classification Subcommittee of the International Headache Society, 2004). Others proposed the term "chronic idiopathic orofacial pain" which should include atypical facial pain, atypical odontalgia, masticatory pain, temporomandibular joint disorder pain and oral dysesthesia (Woda and Pionchon, 2000). The term 'atypical orofacial pain' has also been suggested as a diagnostic term, describing an ongoing, continuous, more or less constant intense chronic pain disorder, frequently of burning quality. Atypical tooth pain is sometimes referred to as "atypical odontalgia", and when the oral mucosa is involved, terms like "oral dysesthesia" and "burning mouth syndrome" are commonly used. Characteristically, an obvious nociceptive substrate is absent (Jacobs et al., 2002). Psychological problems are associated in these forms of pain, although whether these problems are causative or secondary is still subject of debate (Baad- Hansen, 2008). Persistent idiopathic facial pain is currently thought to be neuropathic in nature, especially when the pain is accompanied by paresthesia (Baad- Hansen, 2008). It has also been suggested to be maintained by autonomic sympathic influences.

Patients with chronic orofacial pain frequently undergo numerous dental procedures that fail to eliminate their symptoms (Milam, 1997). Interventions that cause tissue damage, such as endodontic therapy and surgery, may even exacerbate and perpetuate pain symptoms, causing these patients to use (high doses of) analgesics, sometimes even more than considered safe, as well as antidepressants and anxiolytics (Jacobs et al., 2002). Thus, patients with chronic orofacial pain are commonly characterized by multiple diagnoses and inadequate management by multiple disciplines (Israel et al., 2003).

When the patient's daily life becomes dictated by pain, psychological changes and restrictions in lifestyle result in limited capabilities. Therefore, there is a need for early detection of the mechanism(s) underlying the pain state as a basis for rational treatment. As stated by Woolf: "*Perhaps, in the future, when the analgesic armamentarium includes*

*drugs that act on specific mechanisms, it might be possible to judge patient response to these therapies as diagnostic of underlying mechanisms"* (Woolf et al., 1998). The aim of this pilot study was to evaluate the result of a preliminary intravenous diagnostic test based on the response of intravenous administration of different pharmacological probes as possible initiative to distinguish between different pain mechanisms in chronic orofacial pain patients.

## Material and methods

*Patients*

Data for this study were retrieved from the files of consecutive patients with chronic orofacial pain with an ambiguous diagnosis who had attended the Pain Clinic of the University Medical Center Groningen (UMCG) between February 1998 and January 2004 to receive a pharmacodiagnostic test (PDT). Standard examination included history taking with intra- and extra-oral examination. When a dental origin of the pain was suspected, periodontal probing, pulp vitality testing (combining chlorethyl as cold test and hot gutta-percha as warmth test applied to suspicious teeth) and tooth percussion test were performed, diagnostic local anesthesia was given and dental radiographs were taken. When mucosal problems were suspected, periodontal probing was performed, if applicable, diagnostic local anesthesia was given and radiographs were taken. When temporomandibular disorders were suspected, a functional examination was performed, radiographs were taken and if applicable (intra-articular or intramuscular) local anesthesia was performed. These performed diagnostic tests were inconclusive for adequate diagnosis.

A total of 49 patients were tested (46 females and 3 males; mean age at the time of pharmacological testing 43.7 years, SD=11.4). The average pain duration was 8.0 yrs (SD= 6.2), ranging from 1 to 25 years. Of the 49 patients, eleven did not use any medication. Medication used by the other 38 patients varied from paracetamol and NSAID's to opioids and combinations of medication. In table 1, information on the types of used medication is provided.

**Procedure**

To perform the pharmacological test, patients were hospitalized for one day in the UMCG. The test was performed based on a standardized protocol. The following agents were administered intravenously in fixed doses and in a specific order with a ten-minute interval:

| | |
|---|---|
| Saline (0.9%) | 10 ml |
| Saline (0.9%) | 10 ml |
| Phentolamine | 5 mg in 5 min |
| Saline (0.9%) | 10 ml |
| Thiopental | 50 mg in 3 min |
| Saline (0.9%) | 10 ml |
| Fentanyl | 50 µg |
| Naloxone | 400 µg |
| Saline (0.9%) | 10 ml |
| Lidocaine titration | 200 mg in 60 min |

Pain ratings were taken before the test and after each drug or placebo delivery at fixed intervals. Pain intensity was measured using a 100 mm Visual Analogue Scale (VAS) [Priceet al., 1983), the endpoints of which are designated as 'no pain' and 'worst pain imaginable'. In addition, possible side effects occurring during this test were monitored.

*Criteria for pharmacological classification of the patients*
Pain changes were measured by comparing the baseline VAS with the VAS score after each administration. In our study, patients were classified as

placebo responders when 33% or more decrease of pain occurred after at least two placebo administrations

phentolamine responders, thiopental responders or lidocaine responders when there was 33% or more decrease of pain after phentolamine, thiopental responders or lidocaine administration, respectively, without any or with minimal effect in response to placebo administration.

opoid responders when they showed 33% or more decrease of pain after fentanyl administration and increase of pain after subsequent naloxone administration, with no or minimal affect on placebo administration.

When a decrease of pain of 33% or more was measured in two or more active agents, patients were classified into multiple groups. Patients who showed a response of less than 33% to any of the agents administered were classified as non-responders.

To study whether pain medication influenced the classification, patients who used medication were compared with the group without medication. In addition, to study whether classification was influenced by pain duration, the percentage of non responders for different pain durations was calculated. An analysis of variance for repeated measures was performed to study the stability of all placebo injections.

Table 1. Types of medication used with number of patients

| Type | Number of patients |
|---|---|
| Paracetamol | 5 |
| Paracetamol/codeine | 4 |
| Paracetamol /anti convulsant | 5 |
| Non steroidal anti inflammatory drug (NSAID) | 4 |
| NSAID / tricyclic antidepressants | 3 |
| NSAID / paracetamol | 2 |
| NSAID / anticonvulsant | 3 |
| Tricyclic antidepressants | 4 |
| Anticonvulsant | 1 |
| Opioid | 4 |
| Other | 3 |
| Total | 38 |

Table 2. Types en numbers of responders

| Type responder | Responder |
|---|---|
| Fentanyl | 3 |
| Lidocaine | 3 |
| Thiopental | 1 |
| Phentolamine | 2 |
| Fentanyl-lidocaine | 1 |
| Thiopental-fentanyl-phentolamine | 1 |
| Thiopental -phentolamine-lidocaine | 1 |
| Placebo- thiopental -fentanyl-lidocaine | 1 |
| Thiopental -fentanyl-phentolamine-lidocaine | 1 |
| Placebo-fentanyl-phentolamine- thiopental -lidocaine | 2 |
| Fentanyl- thiopental -placebo | 0 |
| Thiopental-fentanyl-lidocaine | 0 |
| Placebo-phentolamine | 0 |
| Non reponders | 30 |
| Total classified | 46 |

Figure 1. Average VAS scores at baseline and after placebo infusions with 95% confidence interval

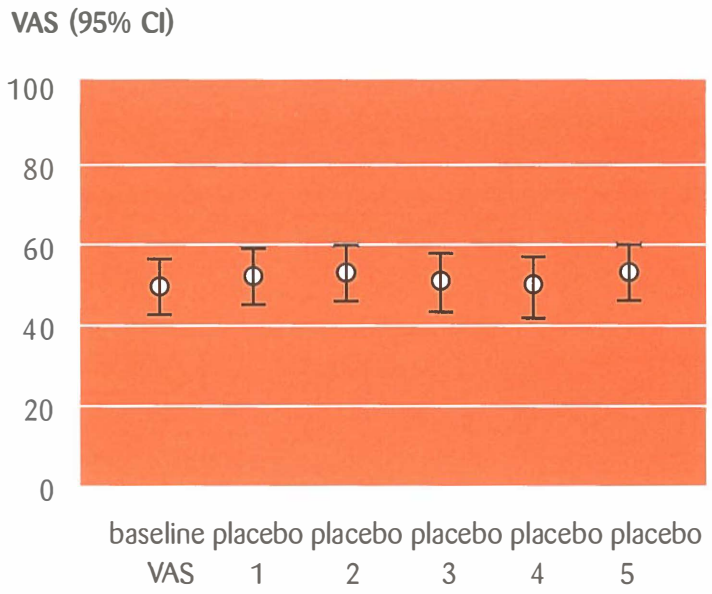
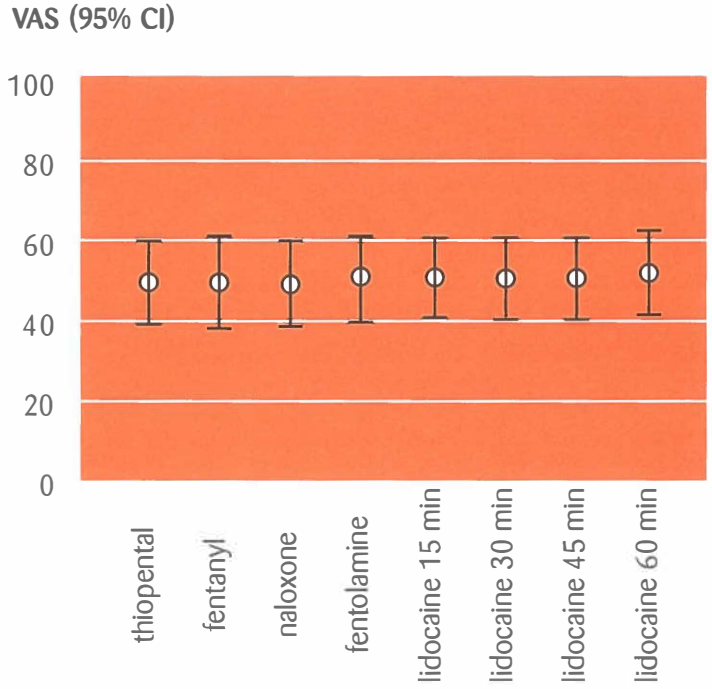



Figure 2. Average VAS scores after drug infusions with 95% confidence interval



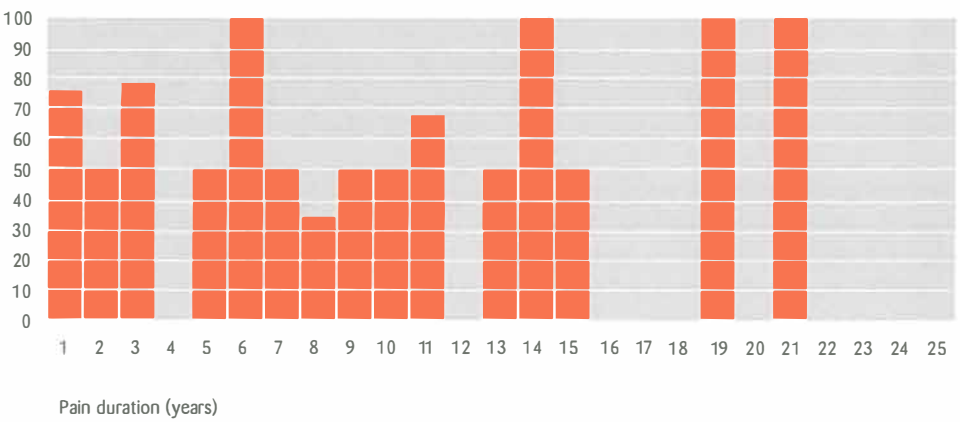
## Results

All included patients were tested without any notable side effects. VAS-scores from the patients were analysed, combining the responses to intravenous pharmacological agents with the above-mentioned criteria. When applying the above-mentioned criteria and because of missing baseline VAS scores of three patients, 46 VAS-scores were available. Sixteen out of these 46 patients could be classified as responder to one or more agents. The remaining 30 patients could not be designated as responder. Data are specified in table 2.

No significant differences were found when the VAS scores following all placebo injections were compared within all subjects (p=0.95). Average VAS scores after placebo infusions are shown in figure 1. Subsequently, figure 2 shows VAS scores after drug infusions. The percentage of non responders in the available pain duration ages is shown in figure 3. Non responsiveness occurred in patients with pain duration varying from 1 year to 21 years.

Of the 'non medication' group, four out of 11 patients could be classified (36%). Of the patients who did consume pain medication twelve could be classified (34%). Types of used medication are described in table 1.

Figure 3. Percentage non responders per available pain duration group



## Discussion

In the management of chronic pain patients, history taking and physical examination will largely contribute to the establishment of a diagnosis. However, when this is not sufficient and additional information is necessary, other means of differentiation are desired. The current study attempted to differentiate chronic pain patients (who could not be differentiated by means of history taking, physical information and other additional diagnostic tests), based on the response on a battery of pharmacological agents. In this study, 16 patients (35%) could be classified into one or more responder groups. The majority (65%), however, could not be classified when using the baseline VAS as reference for classification. Although the percentage of responders may seem disappointing, in this category of patients any additional diagnostic information is of beneficial value. However, due to the retrospective manner of retrieving data, potentially important data, e.g. baseline psychometric measures, were not available in most cases. Baseline data, such as the duration of the pain could be determined for all patients, but did not influence the classification of these patients, as is shown in figure 3.

The responses after administration of the different pharmacological agents have been suggested to be used to determine different pain generating pathophysiological mechanisms (Sörensen et al., 1995; Sörensen et al., 1996; Sörensen et al., 1997; Alvarado, 2006) For instance, fentanyl has been suggested to identify nociceptive pain (Gowing et al., 2003). Fentanyl is a morphine derivate and is 80 to 100 times more potent as morphine (Poklis, 1995 Gowing et al., 2003; Brunton et al., 2006). Fentanyl produces a peak analgesia after 5 minutes (Brunton et al., 2006). The effect of fentanyl should be reversed by its antagonist naloxone to confirm opioid responsiveness, as naloxone antagonizes the toxic and clinical effect of opiates (Brunton et al., 2006). In a recent review, studies report mixed results concerning the effect of opioids on neuropathic pain (Brunton et al., 2006). In particular, fentanyl has been shown to relieve non-cancer neuropathic pain, although very short-time (immediate) effects remain unclear (Dellemijn and Vanneste, 1997).

In neuropathic pain, the nervous system itself has changed either structurally or functionally, and lidocaine has been suggested to eliminate this type of pain (Marchettini et al., 1992; Wallace et al., 1996; Meyerson et al., 1997; Yamamoto et al., 1997; Challapalli et al., 2006). In previous trials, different dosages have been used e.g. 100 mg per patient or individual dosage varying from 1 to 5 mg/kg, either with or without a preceding bolus (Challapalli et al., 2006, Mao and Chen, 2000). In a group of postherpetic neuralgia, no additional benefits were found when 5 mg/kg was used instead of 1 mg/kg (Baranowski et al., 1999). Systemic lidocaine has shown to have no effect on nociceptive pain (Petersen and Rowbotham, 2000; Dirks et al., 2000).

Occasionally, the nervous system may be activated by autonomous input (i.e., sympathetically maintained pain). Phentolamine specifically affects this mechanism (Raja et al., 1991; Arner 1991) and thus is the likely drug to selectively modify this pain mechanism. It is a short-acting, competitive alpha adrenergic receptor antagonist, with tachycardia

and vasodilatation as clinical effects (Brunton et al., 2006). This sympathicolytic procedure was able to predict the effect of subsequent intravenous regional guanethidine treatment with set dosages varying from 5-15 mg (Arner. 1991). Finally, thiopental, a (ultra) short acting barbiturate, is used in a low dose, aiming at centrally mediated pain (Dickinson et al., 2002). It rapidly achieves a therapeutic plasma concentration (Brunton et al., 2006).

Although all the aforementioned mechanisms have been suggested to be affected by specific drugs, caution must be taken when interpreting the short-term effects of the intravenous administration of these drugs. When patients respond to agents, the precise clinical consequence remains unclear. Are all suggested mechanisms involved or do these patients respond to any intervention? Until more scientific data are obtained with regard to these effects, it seems more appropriate to refer to the pain relieving effects as "drug response" rather than influencing specific pain mechanisms.

As the test is done with fixed low doses, again caution must be taken in interpreting the tests' results. These doses may be too low in certain patients to attain a specific effect. In addition, it is not possible to rule out the possibility of carry-over effects, although the VAS scores following all placebo injections remained stable, indicating a similar VAS level prior to all provided drugs and thus suggesting no notable residual effects. Further research should provide further justification for this type of mechanism-based approach in chronic orofacial pain patients.

Previous studies have used other regiments to come to individual dosages, such as calculation of dosages using the bodyweight, or titration until the desired effect (i.e., pain relief), undesired effects (e.g. side effects) or a maximum dosage was achieved. However, titration leads to a longer duration of the test, which may lead to lack of compliance and increased costs. Also, interindividual differences, in e.g. physiology, likely lead to different reactions after and different effects of drug infusion. This may plea for individualisation of the dosages using the patients' bodyweight. In future designs, it may therefore be appropriate to start with a standardized test, which may be followed, if necessary, by an individually tailored test. This individual test could be an elaboration of potential effective drugs, which are subsequently titrated until (un)desired effects are achieved.

To study whether patients' current medication use modified the test outcome, we compared the patients who did not use any medication with the patients who did. In both groups, equal proportions of patients could be classified into responder groups. So apparently, medication use did not influence the ability to classify patients. Relative differences in pain were measured in this test and outcomes may be indicative of a pharmacological approach, which is additional to the current medication used. When a critical reappraisal of current pain medication is warranted, one should refrain from medication (if possible) before testing these patients.

We used a cut-off point of 33% pain relief as being sufficient to provide insight in the

underlying pain mechanism, as on a numeric scale this reduction was found to be associated with a "much better" change (Salaffi et al., 2004; Farrar et al., 2000). Farrar and co-workers also proposed the percentage of 33% rather than the more often used 50% in order to prevent underestimation of research results, especially when this cut-off point is used to obtain insight in the effect of a diagnostic test rather than the efficacy of a treatment (Farrar et al., 2000).

The current design of the test was chosen based on face validity (i.e., does the test intend to measure what we want?). To study the construct validity of this pharmacological test for chronic orofacial pain for the purpose of differentiating between different pain mechanisms, patients diagnosed with only nociceptive pain, only neuropathic pain, and only sympathetically maintained pain, preferably in the orofacial region, should be used. Using a control group without pain would complete the validation (by assessing whether pain free persons perceive pain after injections), although this might be inappropriate from an ethical point of view. In addition, the pharmacological test should be performed twice in a subset of patients to assess intra-individual reliability and consistency.

In summary, with pharmacological testing, disentangling complex chronic orofacial pain problems seems possible in at least a subset of patients. In patients with ambiguous diagnoses, even after thorough examination and/or previous unsuccessful treatment, subtle directions for treatment planning may potentially be provided by this way of testing. Future research should, however, establish the validity and reliability and clinical consequences of the outcomes of this seemingly promising diagnostic tool.

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# The effect of an intravenous diagnostic test on nociceptive, neuropathic and sympathetically maintained pain

*This chapter is based on: The effect of an intravenous diagnostic test on nociceptive, neuropathic and sympathetically maintained pain. Tjakkes GHE. Huddleston Slater JJR, Van Wijhe M, De Bont LGM, Stegenga B. Submitted.*

# 3.3

## Abstract

**Aims:** The purpose of this study was to assess the distinguishing ability of a pharmacodiagnostic test on participants that were clinically diagnosed as having nociceptive, neuropathic, or sympathetically maintained pain (SMP).

**Materials and Methods:** The response to the consecutive intravenous administration of fentanyl, naloxone, phentolamine, lidocaine, alternated with saline, was tested for the three groups of participants, i.e. patients with nociceptive pain, neuropathic pain, and SMP. The responses of the patients to each of the agents were measured using Visual Analogue Scale scores.

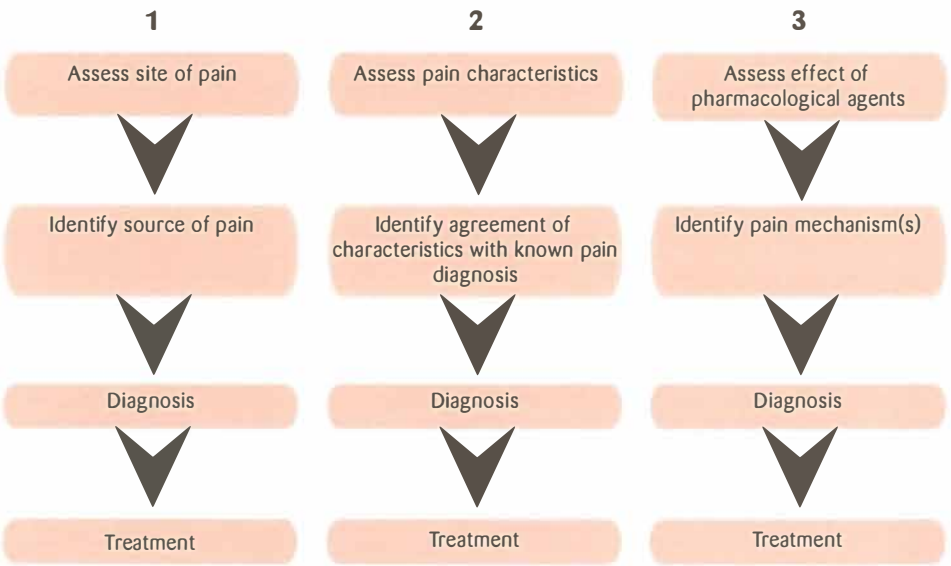
**Results:** 14 nociceptive pain patients; 4 sympathetically maintained pain patients and 10 neuropathic pain patients underwent the test. Using multilevel modelling, the three clinically differing pain groups could be identified. Age appeared to be a confounder with regard to the primary outcome measure, and the coefficients were corrected for this confounding.

**Discussion:** Pharmacological distinction between three different pain mechanisms seems possible using the present pharmacological test. These results may contribute to the diagnostic process in chronic (orofacial) pain patients, where there is a great need for additional diagnostic information. In these patients, pharmacological testing could bring additional insight in occurring pain mechanisms.

## Introduction

Diagnosing orofacial pain conditions often appears to be a difficult task for the clinician. To establish a diagnosis, various strategies are currently used (figure 1). Most frequently, the site of pain perception is used as a first indication for a possible diagnosis. If the site where the pain is felt and the site where the pain originates are the same, it is likely that the diagnosis appears to be correct and the diagnostic process seems to be straightforward. The use of provocation tests (palpation or percussion) and /or local anesthesia tests may help in establishing the source of pain. However, it is rather common in the orofacial area that the site of pain perception does not correspond to the source of the pain (Okeson, 2005). This is mainly due to effects of peripheral and central sensitization, which may easily occur in cases where the pain source is in deep somatic tissues (Okeson, 2005). In persistent and chronic pain, one must be aware of secondary pain phenomena, such as secondary hyperalgesia and pain referral to other sites than where the pain originates. In addition, psychosocial effects are more prominent in these conditions. These factors likely limit the conditions in which this strategy can be applied.

Figure 1. Diagnostic strategies in chronic orofacial pain




In many pain conditions, the pain complaint is presented in a characteristic way. Zakrzewska (2001) has termed these pain characteristics "the nine symptoms of pain" (table 1). For example, the character of the pain, periodicity and severity may be diagnostic for specific pain disorders such as trigeminal neuralgia. In addition, pain may be associated with specific signs. For example, pain occurring on biomechanical function or associ-

ated with jaw movement restriction is suggestive for a musculoskeletal pain disorder. A limitation to this strategy is that the presentation of the pain should not be obscured by non-specific manifestations or sensations, which is usually the case for chronic pain conditions, thus confusing and frustrating the diagnostic process.

A third approach may be the use of pharmalogical agents aiming at specific mechanisms to diagnose the pain. Several pharmacological agents have been described to specifically affect basic pain mechanisms, i.e. nociceptive pain, neuropathic pain, and sympathetically maintained pain (Meyerson, 1997). These drugs could be of assistance in the disentanglement and diagnosis of different chronic pain states, as has been suggested in previous studies (Sorensen et al., 1995; Sorensen et al., 1996 Sorensen et al., 1997). However, for the purpose of additional diagnostic information in orofacial pain conditions, this method has only partly been explored (Scrivani et al., 1999; Baad-Hansen., 2008; Tjakkes et al., 2009).

Recently, a pharmacological diagnostic test has been developed, that calls on the response of pain patient to consecutive pharmacological agents that are administered intravenously. This test has been shown to have the ability to distinguish different responder groups in a chronic orofacial pain population (Tjakkes et al., 2009). Suggestions have been made that the test components affect distinct pain mechanisms. These suggestions are mainly based on theoretical considerations, and partially supported by clinical studies. The validity of the pharmacodiagnostic test has not been studied prospectively.
To enhance the diagnostic process, an alternative strategy is of great importance. Therefore, the aim of this study was to assess the effect of the proposed pharmacodiagnostic test in patients with known types of pain, i.e. nociceptive pain, neuropathic pain, and sympathetically maintained pain.

Table 1. The nine symptoms of pain

| | |
|---|---|
| Character of the pain | What sort of pain is it? |
| Duration/onset time | When did it start? Did it start suddenly? |
| Periodicity | Is there a pattern to the pain? |
| Severity | How severe is the pain, how does it vary? |
| Site | Where do you feel the pain? |
| Radiation | Where does the pain spread? |
| Provoking factors | Does anything make the pain worse? |
| Relieving factors | Does anything make the pain better? |
| Associated factors | Do you notice anything else when you have pain? |

## Materials and methods

*Patients*
Patients that met the diagnostic criteria representing one of the three distinctive mechanisms described below were approached for participation.

*Nociceptive pain patients*
Patients who have their third molars removed typically show a peak in pain one day after the surgery (White et al., 2003). In analgesic efficacy, this pain model is comparable to other postsurgical pain situations (Barden et al., 2004). Patients referred to the department of Oral and Maxillofacial Surgery of the University Medical Center Groningen (UMCG) for removal of two impacted lower third molars were approached to participate in the present study. All eligible participants were informed about the nature of the study and the consequences for participation, i.e. time path, logistics, test procedure, and used agents (as described below). When they agreed to participate, an informed consent was read and signed. After removal of one of the lower third molars, the patients received a new appointment for the removal of the lower third molar on the contralateral side as well as an appointment for performing the pharmacodiagnostic test for the day after the surgical procedure. Patients were instructed not to take any pain medication on the day of test.

*Neuropathic pain patients*
Patients visiting either the department of Neurology or the Pain Management Center of the UMCG with neuropathic pain were approached for participation. For the neuropathic pain mechanism, we included patients that were diagnosed with 1. mononeuropathy (damage to a single peripheral nerve), 2. polyneuropathy (damage to more than one peripheral nerve), or 3. postherpetic neuralgia (chronic pain with skin changes in one or more roots of a cranial root subsequent to acute herpes zoster). The diagnosis was confirmed by an experienced neurologist. When patients agreed to participate, they signed an informed consent.

*Sympathetically maintained pain patients*
For the sympathetically maintained pain (SMP) group, we approached patients to participate who were referred to the Department of Rehabilitation of the UMCG for the management of Complex Regional Pain Syndrome I (CRPS-I). The criteria used for diagnosing CRPS 1 have been described by Veldman (Veldman et al., 1993). In addition, patients from the Pain Management Center of the UMCG who had undergone a sympatheticolytic procedure by means of a successful stellate ganglion blockade or pterygopalatine ganglion blockade with a pain relieving effect (defined by a decrease in VAS score of at least 50%) were invited to participate. When patients agreed to participate, they signed an informed consent.

*Exclusion criteria*
Exclusion criteria for all patients were: pregnancy, age under 18 years, porphyria, and insufficient understanding of the Dutch language.
This study was approved by the Medical Ethical Committee of the UMCG.

*The pharmacodiagnostic test*
To perform the pharmacodiagnostic test, patients were hospitalized for half a day at the UMCG. After confirmation of absence of exclusion criteria, patients were placed on a bed where vital signs (i.e. heart rate, blood pressure, oxygen saturation) were monitored. The patients were provided with a 100 mm Visual Analogue Scale (VAS) to indicate their pain intensity on request (Price et al., 1983). The endpoints of the VAS were designated as 'no pain' and 'worst pain imaginable'. Subsequently, the use of the VAS and the test procedure were thoroughly explained.
A 20-gauge needle was inserted into a suitable vein of the arm and an infusion system was connected.

The following agents were administered intravenously in fixed doses and in a specific order, as indicated below, with a ten-minute interval:

| | |
|---|---|
| Saline (0.9%) | 10 ml |
| Saline (0.9%) | 10 ml |
| Phentolamine | 5 mg in 5 min |
| Saline (0.9%) | 10 ml |
| Fentanyl | 50 µg |
| Naloxone | 400 µg |
| Saline (0.9%) | 10 ml |
| Lidocaine titration | 200 mg in 60 min |

Before and after needle insertion and prior to drug delivery, two baseline pain ratings were taken in order to assess the current pain level. Furthermore, after each drug or saline delivery the pain intensity was assessed with the VAS at fixed time intervals. Any side effects occurring during this test were monitored and recorded.

*Statistical analysis*
For the three groups, the VAS score after each infusion was compared with the average of the two baseline VAS scores. This change was calculated as a percentage increase or decrease. Linear multilevel analysis is an extension of linear multivariate regression analysis, in which it is assumed that there is a hierarchical structure of at least two levels with different properties. For the present study, patients were repeatedly measured over time and these observations within a patient should not be analysed as being independ-

ent. By defining a multilevel hierarchical structure with 2 levels (i.e. amount of pain over time being the highest level, and observations on patient level being the lowest level), a correction is made for the dependency of the observations over time. Thus, a 2-level linear multilevel analysis was executed and in this way regression coefficients were adjusted for dependency and their standard deviations were calculated.

The analysis aims at retrieving a regression equation of the following form:

$$y_{ij} = ß_{0ij} + ß_{1j} + ß_{2j} + e_j \quad (1)$$

in which $y_{ij}$ is the outcome variable, $ß_{0ij}$ is the coefficient of the intercept (in a model that allows a random slope which is comparable to a random effects model, in which i is the $i^{th}$ observation on patient j), $ß_{1j}$ and $ß_{2j}$ are the coefficients of the slopes and $e_j$ is the residual of the $j^{th}$ unit.

As we aimed at distinguishing between three groups, dummy variables were introduced, to "switch off and on" the slope variables; $ß_1$ and $ß_2$ are coefficients of dummy variables. These group dummies introduced for multilevel analysis were as follows:

| | GrpDmy 1 | GrpDmy2 |
|---|---|---|
| Nociceptive pain group | 0 | 0 |
| Neuropathic Pain | 1 | 0 |
| Sympathetic Maintained Pain | 0 | 1 |

So equation (1) for our analysis was as follows:

$$Pain_{ij} = ß_{0ij} + ß_{1j}GrpDmy1 + ß_{2j}GrpDmy2 + e_j \quad (2)$$

in which $Pain_{ij}$ is the VAS score of perceived pain intensity after delivery i in patient j, $ß_{0ij}$ is the coefficient of the intercept (constant) for the ith observation in patient j, $ß_{1j}$ and $ß_{2j}$ are the coefficients of the slopes of group dummies as defined above, and $e_j$ is the residual (error term).

All analyses were executed in MlWin version 2.12. (Centre for Multilevel Modelling, University of Bristol, Bristol, UK). The level of significance was set at $\alpha<0.05$.

## Results

The nociceptive pain group consisted of 12 patients (10 females and 2 males, mean age 22.7, SD 3.7yrs), the neuropathic pain group of 10 patients (8 females and 2 males, mean age 43.4, SD 6.1 yrs), and the SMP group of 4 patients (all females, mean age 44.7, SD 9.7yrs). Neither during nor after the pharmacological testing, any adverse effects occurred and all patients underwent the test uneventfully.

The relative VAS changes, i.e. the percentage change (increase or decrease) after all infusions, compared to the average of the two baselines, were calculated and the results are shown in figure 2. When the results of the separate pain groups are judged, the figure shows that in the sympathetically maintained pain group, the VAS decrease after the phentolamine infusions is larger compared to the previous two infusions. The VAS decreases even more after the fentanyl infusion, with minimal changes after naloxone infusions. The nociceptive pain group shows also a major decrease of VAS after fentanyl infusion. This VAS decrease is less apparent after the subsequent naloxone infusion. Between the three groups, it becomes clear that the effect of the fentanyl infusion is less pronounced in the neuropathic pain patients than in the nociceptive pain and sympathetically maintained pain groups.

Multilevel analysis yielded the following model:

$$Pain_{ij} = ß_{0ij} + ß_{1j}GrpDmy1 + ß_{2j}GrpDmy2 - 1.49\ (0.15)\ Age_j \qquad (3)$$

The regression coefficients listed in table 2 indicate the estimated difference of pain between the groups for the 13 observations and for the 26 participants of the study. For example: the difference, estimated by the model, of a patient from the nociceptive pain group in comparison of a patient of the SMP group is expressed by the value of $ß_{2j}$ if the age is identical:

$$Pain_{ij} = [ß_{0ij} + 0 + ß_{2j}*1 - 1.49\ (0.15)\ Age_j] - [ß_{0ij} + 0 + 0 - 1.49\ (0.15)] = ß_{2j}$$

The statistical significance for all coefficients indicates that the course of the test differs between the three pain groups. Also following from the retrieved equation (3), 'age' appeared to be a confounder, indicating that with increasing age, the perceived pain tends to decrease.

Table 2. Multilevel testing for three groups

| Independent | ß | sd | p |
|---|---|---|---|
| Nociceptive pain group | 58.8 | 3.7 | 0.00 |
| Neuropathic pain group | 62.3 | 3.9 | 0.00 |
| Sympathetically maintained pain group | 69.6 | 5.2 | 0.00 |
| Age | -1.49 | 0.2 | 0.00 |

ß: coefficient sd:standard deviation p: probability

## Discussion

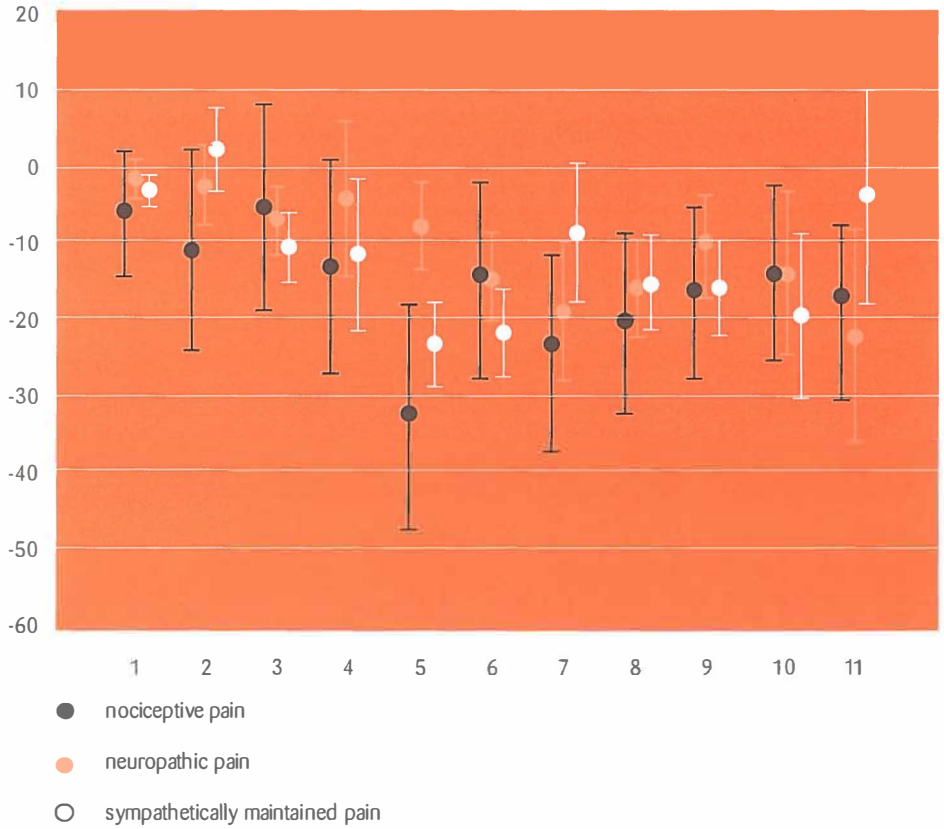
This study examined the effects of administrating different pharmacological agents in patients with different types of pain. As we intended to cover the three most commonly distinguished pain mechanisms (i.e. nociceptive, neuropathic and sympathetically maintained pain), the pharmacodiagnostic test was conducted in patients with specific conditions, mainly based on their clinical characteristics, which are thought to represent these pain mechanisms respectively. Based on a multilevel analysis, the course of the test appeared to differ significantly between the three pain groups.

The patients who had their third molar removed the day before the test were requested to refrain from pain medication intake on the day of the test, as this could affect the pain intensity and, therefore, the baseline VAS, which would make subsequent VAS scoring after drug infusion more complicated. Abstination of medication intake could of course not be obliged, but prior to the test, all patients indicated that they had not taken any analgesic medication. In the neuropathic pain and the SMP groups, the pain diagnoses were made regardless of the use of any medication. To facilitate the patients' willingness to participate and to maintain patients' comfort, we decided not to let the patient stop any medication, in case of medication use.

Despite of possible medication use, all patients that entered the study and underwent the pharmacodiagnostic test perceived pain. Medication use could have been of influence on patient's responses. On the other hand, previous results have shown that medication use did not influence the ability of the test to differentiate between different responder groups (Tjakkes et al., 2009). Moreover, the three pain groups could be differentiated, irrespective of any medication use.

In our study, patients from the three different pain mechanism groups received a series of pharmacological infusions, and VAS pain ratings were obtained. Our test was composed of different pharmacological agents, based on earlier findings. In these studies, nociceptive pain has been identified by fentanyl (Gowing et al., 2003). The effect of the opioid could be reversed by the use of fentanyls antagonist naloxone (Brunton, 2006). For sympathetically maintained pain, phentolamine has been shown to be effective (Arner, 1991; Raja et al., 1991). Finally, the administration of lidocaine has shown to eliminate neuropathic pain (Wallace et al., 1996; Challapalli et al., 2006) In order to account for differences in baseline VAS scores, the relative changes (compared to baseline) were calculated and illustrated in figure 2. By "eyeball judgement" of figure 2, there is a difference in response after the fentanyl infusion between the nociceptive pain and SMP groups on one hand and neuropathic pain group on the other. Between the nociceptive pain group and the SMP group, there tends to be an increase of pain after the naloxone infusion in the nociceptive pain group, whereas the change in the SMP group stays similar. The pain diminishing effects of the administered agents, as would be expected from the different pharmacological agents, on the three pain groups was not undoubtfully confirmed in our study. Because of the relatively small groups, no clear distinctions could be made, based on the separate VAS scores and relative VAS changes for each infusion between the three

Figure 2. Percentual change (S.E.) of VAS score (measured after infusion of the agent) compared to the average baseline VAS




Measurement moment after infusion of the following agents:

| | |
|---|---|
| 1. Saline (0.9%) | 10 ml |
| 2. Saline (0.9%) | 10 ml |
| 3. Phentolamine | 5 mg in 5 min |
| 4. Saline (0.9%) | 10 ml |
| 5. Fentanyl | 50 µg |
| 6. Naloxone | 400 µg |
| 7. Saline (0.9%) | 10 ml |
| 8. Lidocaine | 50 mg |
| 9. Lidocaine | 50 mg |
| 10. Lidocaine | 50 mg |
| 11. Lidocaine | 50 mg |

pain groups.

We used a multilevel model for the analysis of our data. Traditional "single level" models fail when data are hierarchically structured, because the assumption of independence is violated. From a statistical point of view, the application of multilevel analysis has been proven to be more precise. Moreover, it has argued that these models are conceptually enriching (Leeden van der, 1998). Studies in the dental literature often use baseline data and subsequently compare measured values with baseline values. The problem with using regression or correlation between of the change in an outcome value compared to baseline is that of which is called "mathematical coupling", a statistical artefact (Blance et al., 2007). The change can be expressed as a function to the baseline and, therefore, the two values are coupled. In addition to mathematical coupling, the phenomenon of "regression to the mean" may be of concern in these situations (Tu et al., 2007). This occurs with any variable that fluctuates within an individual or a population (due to physiological variation and/or combination with measurement errors). So, preferably a statistical technique is used that incorporates the baseline value(s) into its analysis. The multilevel model to analyse change in relation to baseline without mathematical coupling is the model in which the baseline and follow-up values are specified on one level (level 1), clustered within individuals (level 2) (Blance et al., 2007). Multilevel analysis of previous data of reports on pharmacodiagnostic research may result in alternative conclusions concerning the effect of different pharmacological agents in patients with different pain mechanisms. In our study, we used the VAS values of pain perception as the first level and the patients as the second level. Our model showed that VAS pain scores obtained after pharmacodiagnostic testing from three distinct pain groups did statistically differ from each other, throughout the course of the test.

In addition to the possibility of distinction between the three pain groups, age was found to play a significant role in the equation, indicating that age influences the primary outcome measure (i.e. age is a confounder). So in our sample, with increasing age patients reported relatively lower pain intensities. There is little information about the effect of age on pain experience, but there are suggestions that the similarities between younger and older pain patients are more remarkable than the observed differences (Corran et al., 1997). In chronic pain patients, higher pain ratings were found in a younger cohort when compared to an older cohort. It was suggested that comorbidity in older patients may prompt referral to a pain clinic, resulting in patients with relatively lower pain ratings and pain (Helme, 2001). As our sample consisted of a group of acute pain patients and chronic pain patients, it is unsure whether this explanation may also account for our sample. As in other strategies in the diagnostic process, pain chronicity itself seriously hinders a straightforward assignment of patients into subgroups based on single pain mechanisms. Apart from the peripheral and central changes in the nervous system, the influence of psychosocial factors will be of relatively more influence and should be seriously taken into account (Sessle, 2000). Peripheral sites of action of the administered drugs may play a minor role in these patients due to central, neuroplastic changes. Also, neuronal changes that occur in chronic pain patients appear to affect pain behaviour

(Sessle, 2005). In addition, a shift in the origin of pain from somatosensory input to affective, cognitive and behavioural inputs of pain may take place, which in turn influences the response to the administered drugs (Meyerson, 1997). Therefore, patients should be challenged with an intravenous pharmacological test in a relatively early stage of the existence of pain of unclear origin (preferably before chronicity has been allowed to be firmly established)in order to reveal additional information regarding mechanisms compared to the effect of the test in pain patients with chronic history of extensive duration.

In the test low and fixed doses of drugs were used to minimise adverse effects, to establish a relatively short wash-out period, to prevent carry-over effects, and to make the test not too time consuming. However, due to variations in pharmacokinetics and pharmacodynamics in individuals, it might have been more appropriate to adapt the dosages to the patients' weight to improve the response effect. Another commonly used individual approach is titration of medication. In a titration setting, the dosage is increased until pain relief (or another outcome measure, such as 33% or 50% decrease in VAS pain score), the maximum dosage without sufficient pain relief, or undesired side effects are attained. The consequence is, however, that the washout period will increase, leading to an extension of duration of the test, especially when administration of several medications is desired. It might also have been appropriate to individualize the dosage based on the body mass of each patient and let that dosage be a starting point for a subsequent titration. By individualizing the test dosages, the differential effect(s) of the administered pharmacological agents may become more obvious. Despite the consequence that individualising dosages leads to an extension of the test duration, it is certainly worthwhile to take optimizing measures to change the test-setup in specific patients, as the main goal is to identify, (or even confirm) possible pain mechanisms in patients who suffer from their chronic pain.

Pharmacological pain analysis has previously been used to classify pain within an individual. (Sörensen et al., 1995; Sörensen et al., 1996 Sörensen et al., 1997; Tjakkes et al., 2009). In these studies, patients were hospitalized during several days, receiving one pharmacological agent every day. These agents were titrated until the desired effect (i.e. pain diminishing) or undesired effects (side effects) occurred. For practical reasons, we have used a pharmacodiagnostic test which can be completed within half a day and which would cover different pain mechanisms. When a single drug mechanism is fully tested (using individually tailored dosages, titrating on effect), a more profound statement concerning the effect of the drug can be made. If needed, a subsequent test, using an alternative drug, may be performed.

The challenge, however, lies in obtaining useful additional diagnostic information in patients with a pain condition that cannot be readily classified with existing criteria. This will have a major effect on the assessment of these patients, and it will greatly improve the subsequent treatment modalities. Unfortunately, it is yet not possible to use the current test in a chronic pain patient and to classify this patient into a specific pain group, or to determine the pain mechanisms which are likely in a patient. Also, our study did

not examine the effect of subsequent treatment. Therefore, further research is needed to confirm the usefulness of distinction into three pain mechanisms in chronic orofacial pain patients.

In conclusion, the current study shows that the pharmacological test is able to differentiate between specific pain mechanisms. Future research should aim at identification of the separate test components responsible for this distinguishing capability. The pharmacodiagnostic test may be improved, e.g. by correlating test outcomes with the effect of subsequent treatment, in order to be able to judge the clinical relevance of the test outcomes and predict treatment outcomes. This may enhance the diagnostic armentarium in (chronic) orofacial pain.

*Acknowledgements*
We cordially thank prof. J.B.M. Kuks of the Department of Neurology and prof. J.H.B. Geertzen of the Department of Rehabilitation of the UMCG for permission to include their patients and for their advice.

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# TMD pain: the effect on health related quality of life and the influence of pain duration

*This chapter is based on: TMD pain: the effect on Health related Quality of Life and the influence of pain duration. Tjakkes GH, Reinders JJ, TenVergert EM, Stegenga B. Published in Health and Quality of Life Outcomes 2010: 2; 8:46.*

# 4.1

## Abstract

**Aims:** As impact of literature concerning this subject is scarce, the objectives of this study were to assess whether the health related quality of life (HRQoL) is decreased in patients with painful temporomandibular disorders (TMD) as compared to the HRQoL in the general population, and to evaluate to what extent pain duration affects HRQoL.

**Methods:** Data concerning physical and mental health were retrieved from patients with painful temporomandibular disorders. Assessment tools used were: the Mandibular Function Impairment Questionnaire, the Short-Form-36 (SF-36), the Hospital Anxiety and Depression Schedule, and the General Health Questionnaire. In order to examine the influence of the duration of pain on HRQoL, the total sample was divided into three different subgroups. Subgroup 1 consisted of patients with complaints existing less than one year. Patients with complaints from 1 to 3 years were allocated to the second group. The 3rd subgroup included patients with complaints longer than 3 years.

**Results:** The total sample consisted of 95 patients (90 females and 5 males). On most physical and social functioning items, groups 2 and 3 scored significantly worse than the general population. On the other hand, none of the groups differed from the general population when comparing the mental items. Duration of pain was significantly correlated with SF-36 subscale physical functioning and the mandibular impairment.

**Discussion:** Patients with TMD pain less than one year score better than compared to the population norm. With a longer duration of pain, mental health scores and role limitations due to emotional problems do not appear to be seriously affected by reduced physical health, while social functioning appears to be considerably affected.

## Introduction

Temporomandibular disorders (TMD) comprise a group of disorders that affect the temporomandibular joint (TMJ), the masticatory muscles, or both. TMD involve musculoskeletal pain, disturbances in the mandibular movement patterns, and / or impairment in functional movement (Stegenga, 1991). Pain is the main characteristic of most TMD and also the main reason for patients to seek treatment (Dworkin, 2006). Many TMD should be considered chronic pain conditions, since they show lot of similarities (Dworkin and Massoth, 1994). Psychological factors have been implicated in the initiation as well in the perpetuation of several TMD (Yap et al., 2002). Stress, somatic distress, and depression may be potential etiological risk factors for TMD-related pain (Zakrzewska and Harrison, 2002). When the duration of pain increases, psychological factors may become more obvious and prominent. Even after a decrease of the somatosensory input, suffering and pain behaviour may continue and even increase (Okeson, 2005).

It is generally accepted that quality of life is negatively affected by chronic pain (Kempen et al., 1997; Schlenk et al., 1998). The impact of TMD (and other types of orofacial pain) on health related quality of life (HRQoL), however, has scarcely been described. Recently, Naito et al. conducted a systematic review on oral health status and health-related quality of life (Maito et al. 2006). They found only one study concerning TMD. In this study, Reisine and Weber observed a sample of 30 patients with temporomandibular disorders, during 6 months (Reisine and Weber, 1989). Different aspects of HRQoL were investigated e.g. anxiety, perceptions and social functioning. It was found that while the pain decreased over time, oral and functional aspects did not improve significantly within the same period of time. This result may be due to a slower response of other parameters to treatment in contrast to a relatively rapid response of pain. Furthermore, the authors found relatively poor ratings of well-being and high levels of anxiety, suggesting that TMD patients are characterized by relatively negative psychological states, and that when pain persist (even when diminished) functional aspects do not improve.

Murray and collegues described the HRQoL, as measured with the Oral Health Impact Profile (OHIP), of patients referred to a craniofacial pain unit because of TMD and facial pain (Murray et al., 1996) With regard to pain-related disability and HRQoL, 29.7 % of the sample reported a frequently disturbed sleep as a consequence of their oral conditions, and 36.4 % reported feelings of depression. Different researchers have found a larger impairment of the oral HRQoL in TMD patients compared with healthy population, using the OHIP (Segu et al., 2005; John et al., 2006).

LeResche and collegues studied the facial expression as well as states of anxiety, depression, somatization and daily stress in a group of TMD pain patients, subgrouped into a chronic and non-chronic category (LeResche et al., 1992). With regard to these four aspects of HRQoL, no differences were found between a group of patients that perceived pain for the first time within the last two months (non chronic group) and a group that suffered from pain for over 6 months (chronic group).

It is not clear whether and, if so, how (chronic) pain related to TMD influences HRQoL, and whether pain duration is of influence. It may be hypothesized that when pain has just begun, this will mainly affect physical factors such as physical functioning. When the pain lasts for a longer period, and treatment so far has failed to relieve the pain, it may start to have more impact on the emotional behaviour, social factors and HRQoL. However, whether this is the case is yet not clear. Information concerning the influence of pain and its persistence on HRQoL may guide treatment in these patients. Therefore, the aims of this study were to assess whether the HRQoL is decreased in orofacial pain patients as compared to the general population, and to study the effect of duration of pain on HRQoL.

## Methods and Materials

*Sample*

Patients were recruited from the department of Oral and Maxillofacial Surgery of the University Medical Center Groningen (UMCG). The group consisted of 95 patients consecutively consulting the TMD/Orofacial Pain section for their orofacial pain problems. The inclusion criteria were age over 16 years, no language barrier, and the presence of a painful temporomandibular disorder as classified according to the RDC/TMD (Dworkin and LeResche, 1992; Lobbezoo et al., 2005). From the axis II information, the duration and impact of the pain were assessed. The influence of the duration of pain on HRQoL was examined by two means. Firstly, the total sample was divided into three different subgroups. Subgroup 1 consisted of patients with complaints existing less than one year. Patients with complaints from 1 to 3 years were allocated to the second group. The third subgroup consisted of patients with complaints longer than 3 years. Secondly, the influence of the duration of pain was studied using results of the total sample in regression analysis. During their first visit to the clinic, patients were informed about the study and the content of the questionnaires. When patients were willing to participate, they were requested to fill in an informed consent.

Quality of life has been described by the World Health Organisation as " ... an individual's perception of their position in life in the context of the culture and value system of which they live with the relation to their goals, expectations, standards and concerns." This concept incorporates different aspects of individuals, including physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of the environment (WHOQoL, 1995).

*Assessment and Instruments*

During the second visit to the clinic, patients were instructed how to complete the questionnaires. Subsequently, patients were left alone to complete the questionnaires. When necessary, unclear test items could be clarified by the interviewer. Only Dutch versions of the questionnaires were used.

HRQoL was measured by the following instruments.

**SF-36:** The Medical Outcome Short Form Health Survey, a 36 item health survey, was used to assess the patients' HRQoL (Hays et al. 1993). It includes eight health concepts: physical functioning (PF, measuring the physical activities), role limitations due to physical health problems (RP, measuring the effect of the physical health on work and daily activities), bodily pain (BP), general health (GH) perceptions, vitality (VT, measuring energy/fatigue), social functioning (SF), role limitations due to personal or emotional problems (RE, measuring the effect of the emotions on work and daily activities) and general mental health (MH including anxiety and depression). The scores on every subscale range from 0-100, with higher scores indicating better health states. Reference values were used to compare the results of the group in question. The reference values were taken from a Dutch study, which consisted of a random Dutch sample of 1742 persons,

which is used as the reference group (Aaronson et al., 1998). In this study the mean values for each subscale were for PF 83.0 (sd 22.8), RP 76.4 (sd 36.3), BP 74.9 (sd 23.4), GH 70.7 (sd 20.7) VT 68.8 (sd 19.3), SF 84.0 (sd 22.4), RE 82.3 (sd 32.9), MH 76.8 (sd 17.4).
**MFIQ:** The Mandibular Function Impairment Questionnaire was used to obtain information about the function impairment of the jaw. It was developed to provide for a tool, additional to the clinical assessment, for assessment of function impairment in the patients own value system (Stegenga et al., 1993). It comprises 17 items, concerning mandibular functions e.g. speaking and eating different types of food. A functional impairment rating score (FIRS) can be retrieved. This is a score ranging from 0 (no function impairment) up to 5 (indicating severe function impairment).
**HADS:** To assess depression and anxiety in a hospital setting, the HADS was used. To screen for anxiety (HADS-A) the odd items were used. For the screening of depression (HADS-D), the even items of questionnaire were used. On each subscale, scores up to 7 indicate no signs of anxiety or depression, scores between 8 and 10 suggest probable anxiety or depression, and scores over 10 indicate the presence of anxiety or depression, respectively (Zigmond and Snaith, 1983).
**GHQ-28:** The general health questionnaire was used to assess different types of psychiatric distress. It is a 28 item list which can be divided into four different subscales: somatic symptoms (GHQA), anxiety and insomnia (GHQB), social dysfunction (GHQC) and severe depression (GHQD) (Goldberg and Hillier, 1979). The reference values were for GHQA 6.2, GHQB 5.8, GHQC 7.0, GHQD 1.6 and were retrieved from a general Dutch population of 485 persons (Koeter and Ormel, 1991).

*Sample size calculation*
To estimate the a priori sample size, an effect size of 0.4 was chosen. By convention this effect size is considered as a moderate effect size. Sample was calculated on an ANOVA with the parameters α, ß, number of groups and effect size. α was set at 5%, ß at 10%, number of groups 3, resulting in a critical F of 3.10931. The total calculated sample was 84. To account for possible dropouts, sample size was about 10% increased to 95.

**Statistical analysis**
Descriptive statistics were performed to summarize sample characteristics. Data were tested for normality using the Kolmogorov-Smirnov test. By means of one sample t-tests, the HRQoL scores of the patients were compared to those of a general population. To test mean differences in HRQoL among subgroups, one-way ANOVA was carried out, followed by Scheffe's post hoc multiple comparison test in case of a significant result. In order to study the association between the duration of pain and the scores on the different SF-36 subscales, HADS scores, GHQ-28 scores, and MFIQ score, respectively, Pearson correlation coefficients were calculated. Outlier analysis with scatter plots was performed to look for possible difference in scores between female and male participants. Data from the total sample was analysed in a regression analysis. Data were analyzed using SPSS 14 (SPSS Inc, USA). The level of significance was set at 0.05. This study was approved by the Medical Ethical Committee of the UMCG.

## Results

*Patients*
In total 95 patients (90 females and 5 males) provided their consent to participate in the study. Their average age was 40.3 yrs (sd 13.1, ranging from 17-69). According to the RDC/TMD, patients were diagnosed with a group I diagnosis (myofascial pain), a group II diagnosis (disc displacement) a group III (arthralgia, osteoarthritis and osteoarthrosis). A group I diagnosis was established in 31.9%; a group II diagnosis in 4.4% and a group III in 35.2%. A combined diagnosis was made in 28.7% of all cases (in 7.8% group I and II, in 17.6% group I and III, and in 3.3% group II and III were combined). Furthermore, the participants of the 3 subgroups based on pain duration were calculated: subgroup 1 (pain present for less than one year) consisted of 15 patients (14 females; 1 male, mean age 37.7 yrs, sd 14.4, range 17-69), subgroup 2 (1-3 years pain duration) consisted of 16 patients (13 females, 3 males; mean age 37.5 yrs, sd 14.1, range 20-68), and subgroup 3 (more than 3 years of pain) consisted of 64 patients (63 females, 1 male; mean age 41.6 yrs, sd 12.5, range 17-67). The distribution of the diagnoses, medication use and coinciding chronic pain diseases among the three groups is listed in table 1.

**Effects of pain duration: Three groups**

*Results compared with reference values*
Table 2 shows the mean SF-36 and GHQ scores for the three subgroups. The first ("relatively acute") subgroup scored better on the subscale physical functioning and worse on subscales general health and vitality than the general population, but on the other subscales this subgroup and the general population revealed comparable scores.
Compared with the general population, the second subgroup scored worse on four subscales (bodily pain, vitality, general health and social functioning) and the third subgroup scored worse on six SF-36 subscales *(bodily pain, vitality, general health, social functioning, physical functioning and role emotional).*
In the first and second group, scores on the GHQ scales did not significantly differ from scores in the general population. The third group showed more impairment in somatic symptoms and showed higher social dysfunction, with worse scores on GHQA and the GHQC, compared to those obtained from the general population.

*Comparisons between groups*
No differences were found in age between the three groups. Statistically significant differences were found between groups 1 and 3 with regard to the SF-36 subscore on the scales *physical functioning* and *bodily pain* (i.e. scores were better in group 1), but not between groups 2 and 3. Other SF-36 scores did not differ significantly between the three groups.
The third group showed more somatic problems as well as a higher level of social dysfunction compared to the first group, as GHQA and GHQC scales revealed significant differences between these groups.
The patients' impairment in mandibular function, as assessed with the MFIQ and ex-

pressed in the FIRS, was 2.4 (sd 1.1) for the first group, 2.6 (sd 2.0) for the second group, and 3.3 (sd 1.6) for the third group, indicating moderate impairment in these three subgroups (table 2). No significant differences between the three groups were found in the FIRS.

Both HADS-A and HADS-D scores were worse in groups 2 and 3 as compared to group 1 (table 3). In addition, the HADS-D score in group 2 was worse than in group 3.

**Effects of pain duration: total sample**

The social, psychological and part of the physical measures did not show significant correlation with pain duration. Of all calculated correlations, the SF-36 subscale *bodily pain* and the FIRS were significantly correlated with the duration of pain.

Outlier analysis revealed no differences on the subscales in any of the assessed subscales between female and male patients.

Table 1. Distribution of age, RDC diagnoses medication usage and coinciding chronic pain disorders among the three subgroups

| Group | 1 | 2 | 3 |
|---|---|---|---|
| Total | 15 | 16 | 64 |
| Female/male | 1/14 | 3/13 | 1/63 |
| Age (sd) | 37.6 (14.4) | 37.5 (14.1) | 41.6 (12.5) |
| **RDC/TMD diagnosis:** | n | n | n |
| Group I | 3 | 8 | 20 |
| Group II | 0 | 0 | 3 |
| Group III | 5 | 7 | 24 |
| Group I + group II | 0 | 0 | 4 |
| Group I + group III | 5 | 0 | 12 |
| Group II + group III | 2 | 1 | 1 |
| **Analgesic usage** | | | |
| Paracetamol | 0 | 1 | 7 |
| NSAID | 1 | 0 | 3 |
| Tricyclic antidepressant | 1 | 5 | 6 |
| Tricyclic antidepressant + paracetamol | 1 | 0 | 0 |
| Tricyclic antidepressant + NSAID | 0 | 0 | 2 |
| NSAID + opioid | 0 | 0 | 2 |
| **Other chronic pain condition** | | | |
| Rheumatoid arthritis | 0 | 2 | 1 |
| Hernia | 0 | 0 | 1 |
| Back pain | 0 | 0 | 1 |

Group 1: Myofascial pain
Group 2: Disc displacement
Group 3: Arthralgia/osteoarthritis/osteoarthrosis
NSAID: Non-steroidal anti-inflammatory drug

Table 2. SF-36 and GHQ scores in three groups of orofacial pain patients and reference values

| | Reference | 1 | 2 | 3 |
|---|---|---|---|---|
| Scale | Mean (SD) | Mean (SD) n=15 | Mean (SD) n=16 | Mean (SD) n=64 |
| SF-36 PF[a] | 83.0 (22.8) | 92.1 (8.1)* 3 | 74.2 (33.1) | 72.3 (25.7)* 1 |
| SF-36 RP[a] | 76.4 (36.3) | 54.2 (38.1) | 71.2 (3.6) 3 | 41.2 (39.7) *2 |
| SF-36 BP[a] | 74.9 (23.4) | 66.1 (20.4) 3 | 53.2 (27.5) * | 48.5 (19.7) *1 |
| SF-36 GH[a] | 70.7 (20.7) | 53.0 (23.4)* | 55.8 (18.7) * | 54.4 (20.6) * |
| SF-36 VT[a] | 68.8 (19.3) | 52.9 (14.9)* | 49.3 (21.6) * | 55.2 (19.4) * |
| SF-36 SF[a] | 84.0 (22.4) | 74.0 (22.9) | 66.0 (29.2)* | 66.7 (23.4) * |
| SF-36 RE[a] | 82.3 (32.9) | 66.7 (31.8) | 81.0 (55.0) | 80.9 (34.1) |
| SF-36 MH[a] | 76.8 (17.4) | 66.4 (12.5) | 60.6 (17.9) 3 | 73.2 (13.0) 2 |
| GHQA[b] | 6.2 | 6.7 (4.1) | 6.3 (4.1) | 8.2 (4.0) * |
| GHQB[b] | 5.8 | 2.8 (2.1) 2 | 7.5 (3.6) 1 | 5.9 (4.4) |
| GHQC[b] | 7.0 | 6.6 (1.8) 3 | 8.2 (3.3) | 8.3 (2.3) *1 |
| GHQD[b] | 1.6 | 0.8 (1.8) | 2.7 (3.5) | 1.9 (3.0) |

Values in mean (standard deviation, * $p<0.05$ from reference values, in superscript the the group to which the value is statistically different; reference values from [a] Aaronson et al.1998, [b] Koeter and Ormel, 1991.

(PF, physical functioning; RP, Role limitations physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role limitations emotional; MH, mental health; SD, standard deviation; GHQA, somatic symptoms; GHQB, anxiety and insomnia; GHQC, social dysfunction; GHQD, severe depression; P, P-value)

Group 1: complaints of one year or shorter
Group 2: complaints within 1 and 3 years
Group 3: complaints longer than 3 years

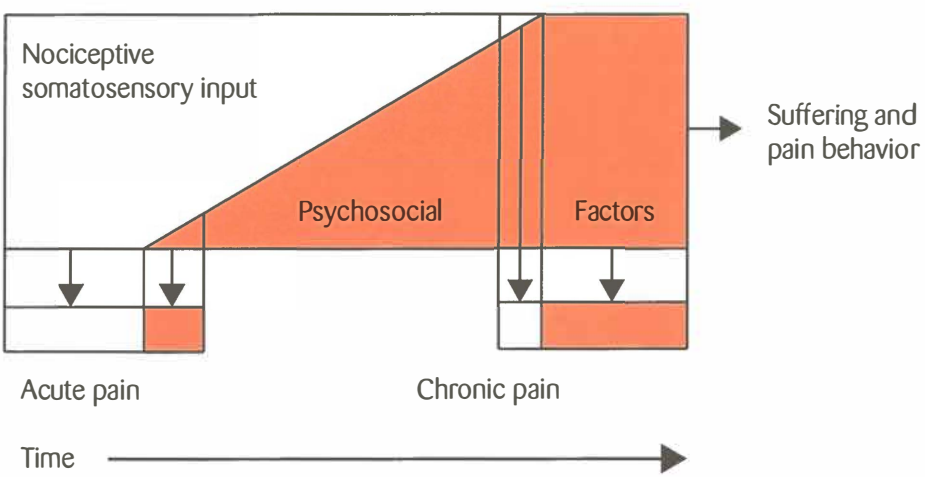
Table 3. FIRS, HADSA and HADSD scores (standard deviation) for three groups

| score | Group 1 | Group 2 | Group 3 |
|---|---|---|---|
| FIRS (sd) | 2.4 (1.1) | 2.6 (2.0) | 3.3 (1.6) |
| HADS A (sd) | 3.3 (1.8) [2,3] | 6.4 (4.1) [1] | 5.0 (3.6) [1] |
| HADS D (sd) | 1.6 (1.1) [2,3] | 6.2 (4.2) [1,3] | 3.5 (3.1) [1,2] |

Group 1: complaints of one year or shorter
Group 2: complaints within 1 and 3 years
Group 3: complaints longer than 3 years

(FIRS; functional impairment rating score, HADSA; anxiety, HADSD; depression. In superscript the group to which the value is statistically different)

Figure 1




The effect of duration of symptoms on psychosocial factors. From Okeson (Okeson, 2005). Used with permission.

## Discussion

In this study we examined whether the duration of pain in TMD patients seeking treatment affects the HRQoL and psychological well-being. When managing these patients, psychological assessment may lead the clinician to multidimensional, biobehavioral therapy modalities rather than to somatically based therapies (Dworkin, 2006). Also, TMD patients classified into different cognitive-behavioural profiles seem to respond differently when the same treatment is offered (Dahlstrom et al., 1997). Thus, not only the physical but also the psychological status may influence the treatment outcome.

The duration of pain is thought to have a significant impact on a patient's psychological status (figure 1) (Okeson, 2005). To provide more insight into the effect of duration of pain complaints, we compared patients with relatively acute pain (less than 1 year) and patients with chronic pain (1-3 years and > 3 years, respectively). A striking finding was that in all three subgroups the SF-36 scores of the subscales *role emotional* and *mental health* did not differ significantly from the reference values. It may be that patients with a longer experience of complaints tend to get used to their pain and symptoms and incorporate them as a part of their life, thereby leaving their mental health less affected.

The first group did score significantly higher ("better") on the subscale *physical functioning*, compared to the population norm. This finding could be explained by possible underestimation of the physical situation, when patients visit a hospital and are allocated to a study group that answers questions about health. Patients with pain or function problems that have arisen within the last year, may tend to focus on these problems in an opposite manner than patients who have a longer experience with these problems. In addition, the scale bodily pain was not significantly different from the reference value. Because of the relatively short existence of pain, patients may underestimate or underrate the consequences of their disorders on the measured scales. They may be convinced that (pain) symptoms will be transient and, therefore, patients will not allow them to affect the physical items. Patients may also feel the need to convince the doctor that the symptoms are purely physical, and want to display that statement in the answers of the subscales.

By contrast, on SF-36 physical health items *bodily pain, general health* and *vitality* the second and third group scored significantly worse than reference values. In addition, in the third group the items *physical functioning* and *role physical* were also worse than reference values. This physical impairment was confirmed by the FIRS scores, indicating moderate function impairment. So the mandibular function was lowered in all three groups. The GHQA score, which represents the somatic general health, is significantly lower ("worse") in the third group, which is in accordance with the scores on the SF-36. With significantly lower scores on the physical scales of the SF-36, the second and third subgroup did not score significantly lower on the mental scales.

Between the different pain duration groups, statistically significant differences were

found only on a few scales. Comparing "better" scores from the first group with "worse" scores from the third group, leads in the *physical functioning* subscale to a significant difference between those scores. Although the HADS scores are interpreted using cut-off points, it is striking that the depression scale (HADS-D) in group 2 is not only higher compared to group 1, but also compared to group 3. Patients who experience complaints for a short time may not be seriously affected, but when pain persists, psychological distress will be more pronounced. Later, when patients are used to the pain or when they are sufficiently reassured about their health status, the psychological distress will return to lower values again. This is in accordance with the score on the *mental health* subscale of the SF-36, which is better in the third group compared to the second group.

According to our findings, it may seem that patients with a shorter duration of pain seem to underrate their physical impairment or at least do not consider it to be relevantly impaired, as the scores are "better" compared with a healthy reference group. Patients with longer lasting pain at least longer than one year, have more pronounced physical problems. The role limitations due to emotional problems or the mental health seem to be hardly affected, however. It has been suggested that psychological functioning is merely related to patients' beliefs and coping strategies rather than to the physical impairment (Turner et al., 2001). On the other hand, the social functioning scale in the SF-36 as well as the GHQC score suggest that social functioning is affected in the third group. This may be explained by role limitations due to physical limitations, which in turn may be the result of the actual disorder.

In addition to the analysis with three subgroups, we calculated Pearson correlation coefficients with data from all patients. This revealed a significant correlation between the whole range duration of pain with the subscale *physical functioning* and the mandibular impairment (FIRS). So with a longer duration of pain, the somatic well-being is considered worse. It remains unclear whether the physical discomfort has worsened during its existence or whether the discomfort is only rated worse due to its longer existence. Other subscales and other scores did not show significant correlation with duration of pain, which may be explained by a large range of duration of pain in contrast to the smaller scale range of the scores on other subscales and the other questionnaires.

One factor that may be of influence on the results is the age. In our sample, no difference was found between the three groups. Besides TMD pain, other pain condition could play a role in HRQoL. Of the studied sample totally five had an accompanying chronic condition. In the second group, two suffered also from rheumatoid arthritis. In the third group, one patient suffered from rheumatoid arthritis, one from hernia and one from low back pain. These conditions could have influenced the questionnaire outcomes, although the number of patients is a slight minority compared to the total sample size, therefore we argued this to be of negligible influence.

A limitation of this study could be the large female predominance, compared to the general population, which may hamper the generalizability of the results. However, a

predominance of female gender in TMD is also found in epidemiological research (LeResche, 1997). In addition, more female than male patients seek treatment for their pain problems, leading to an increasing female predominance in specialist centers, with a female:male ratio ranging from 2:1 to 9:1 (Bush et al., 1993). In addition, outlier analysis (to explore possible differences in measurements in our sample between male and female patients) revealed no outliers in the assessed subscales. We thus consider sex difference in our sample to be of minor influence and we therefore decided to include both male and female in the total analysis.

In patients with chronic pain conditions, such as most TMD pains, it has been demonstrated that psychological factors are better predictors of treatment outcome on the long-term than physical findings are (Dworkin, 1994, Turk and Okifuji, 2002). When TMD patients with pain less than one year are compared to a reference population, it was found that these patients scored better on physical functioning. However, we found that patients with longer lasting problems have more pronounced physical problems and limitations and that these limitations have impact on social functioning in this group. The mental health and role limitations due to emotional problems do not seem to be seriously affected by reduced physical activities. Especially in cases of longer duration of pain, where initial treatment has failed to relieve the pain, the social functioning may be considerably affected and should therefore be taken into account when managing these conditions.

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# The effect of orofacial pain on quality of life as measured by different standardized measurement instruments compared with individual measurements

*This chapter is based on: The effect of orofacial pain on Quality of Life as measured by different standardized measurement instruments compared with individual measurements. Tjakkes GH, Reinders JJ, Elisabeth M. TenVergert EM, Huddleston Slater JJR, Stegenga B. Submitted.*

# 4.2

## Abstract

**Aims:** The purpose of this study was to explore whether a short, individualized approach reveals different information as compared to the use of standardized measurements of mental health and health related quality of life (HRQoL) in orofacial pain patients.

**Materials and Methods:** Different standardized measurement instruments, assessing concepts which are likely related to HRQoL, were used. For the individualized approach, patients were asked to indicate and rate a domain that most influenced their health related quality of life and to rate their overall HRQoL with a mark. The results of both methods were combined, by calculating correlation coefficients.

**Results:** When patients were asked to depict a domain that influences their HRQoL, the domains *health* and *family* were indicated most frequently. When comparing the results from the individualised and the standardized instruments, only the ratings from the domain *health* were significantly correlated with the Short Form-36 subscale *mental health*. These results suggest that a standardized assessment reveals different information than individualized assessment.

**Conclusion:** In assessing the mental health and HRQoL in chronic orofacial pain, a standardized assessment is preferably combined with an individualized assessment, which may lead to a more complete appraisal of the HRQoL of pain patients.

## Introduction

Orofacial pain is a common complaint for patients to visit the dentist. Mostly, these cases are transient in nature, and a diagnosis will be relatively easy to establish with subsequent offered treatment. However, in persisting orofacial pain, neuroplastic changes may occur and also, psychosocial factors become more prominent (Okeson, 2005). To assess the influence of these psychological distress and social effects, specific, standardized psychological measures can be used. Examples of measures used are the Hospital Anxiety Depression Scale (HADS) and the General Health Questionnaire (GHQ). In addition, gaining popularity in health assessment, quality of life (QoL) is an increasingly used measure of overall well-being. QoL has been described by the World Health Organisation as "... an individual's perception of their position in life in the context of the culture and value system of which they live with the relation to their goals, expectations, standards, and concerns." This definition incorporates different aspects of individuals, including physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of the environment. An often used, standardized QoL instrument is the Short Form-36 (SF-36).

In the assessment of health related quality of life (HRQoL), a distinction between two different approaches can be made, namely the "*need* approach" and the "*want* approach", differentiating between what someone needs and what someone wishes (Häyry, 1991). In the *need* approach it is assumed that HRQoL is determined by certain needs, such as health and physical performance. These needs are often considered to be conclusive. Hence, in this approach, HRQoL is measured by means of standardized questionnaires that include measurement instruments to assess these needs. On the other hand, the *want* approach allows the view of the individual, using values or factors that determine the person's HRQoL (Häyry, 1991). In the past, instruments aiming at an individual approach of HRQoL have been developed. (Jambon and Johnson, 1997; Schwartz and Sprangers, 1999) These methods were based on the assumption that the individual is the best source for judging quality of life aspects which may be different for each individual (Browne et al., 1997). So this approach uses an individual approach without predefined factors.

In general, patients with (chronic) painful conditions not only perceive the pain but also experience suffering. Thus, assessing the patient's perception of how the pain affects life might provide information of the extent of suffering, as the quality of life in chronic pain patients may be related to different factors or domains that are not exclusively related to the pain. It is assumed that oral health and quality of life are inextricably connected (Gift and Redford, 1992). Nevertheless, the exact connection between health and QoL is unclear. Although one might expect that when (oral) health is negatively affected, the QoL will subsequently decrease as well. This consequence is not self-evident. People with chronic disabling disorders may perceive their QoL better than healthy controls (Allen, 2003). This may be due to the phenomenon that a subject's attitude towards the perceived QoL may change overtime, making the QoL a dynamic construct (Allison et al., 1997).

In the assessment of chronic orofacial pain patients, it is generally accepted that a multiaxial approach is a prerequisite to appropriately manage these patients. Given the variety in methods for measuring psychological distress and HRQoL, it is clear that these concepts are hard to grasp with one method. It is for instance not clear whether they should be assessed individually or standardized. In standardized measurements appropriate domains for the individual patient may lack and, in addition, in individual measurements, "need" items may be overlooked.

The purpose of this study was to explore whether a short, individualized approach in quality of life assessment in orofacial pain patients reveals corresponding or other information when compared to the information obtained from standardized measurements. The central focus of this study is to investigate the convergent and divergent validity of the individualized measurements of mental health and HRQoL.

## Methods and Materials

*Patient selection*
Patients from the section for Temporomandibular Disorders / Orofacial Pain from the department of Oral and Maxillofacial Surgery of the University Medical Center Groningen (UMCG), older than 16 years and without language barrier were asked to participate in a study concerning their quality of life. Patients willing to participate gave their informed consent and were classified according to the research diagnostic criteria for temporomandibular disorders (RDC/TMD; Dworkin and LeResche, 1992).

*Assessment and Instruments*
*Standardized approach*
Generic measure: The Short Form-36 (SF-36), is a 36-item HRQoL questionnaire. (Hays et al., 1993, Aaronson et al., 1998) It includes eight health-related concepts: physical function (PF, measuring the physical activities), bodily pain (BP), role limitations due to physical health problems (RP, measuring the effect of the physical health on work and daily activities), role limitations due to personal or emotional problems (RE, measuring the effect of the emotions on work and daily activities), general mental health (MH, including anxiety and depression), social functioning (SF), vitality (VT, measuring energy/fatigue) and general health (GH) perceptions. The scores on every subscale range from 0-100, with higher scores indicating better health states.

Specific measures: The Mandibular Function Impairment Questionnaire (MFIQ) was used to obtain information about the function impairment of the jaw. It was developed to provide for a tool additional to the clinical assessment, for assessment of mandibular function impairment in the patient's own value system (Stegenga et al., 1993) This is believed to be of value of the quality of functioning in this group of patients. It comprises 17 items, concerning mandibular function e.g. speaking and eating different types of food. A functional impairment rating score (FIRS) can be retrieved. This is a score ranging from 0 (no function impairment) up to 4 (indicating severe function impairment).

To assess depression and anxiety in a hospital setting, the Hospital Anxiety Depression Scale (HADS) was used (Zigmond and Snaith, 1983). On each of the two subscales (HADS-A representing anxiety, HADS-D representing depression), scores up to 7 indicate no signs of anxiety or depression, scores between 8 and 10 suggest probable anxiety or depression and scores of greater than 10 indicate the presence of either anxiety or depression.

The General Health Questionnaire was used to assess different types of psychiatric distress. This 28-item questionnaire yields scores on four domains, i.e. somatic symptoms (GHQA), anxiety and insomnia (GHQB), social dysfunction (GHQC) and severe depression (GHQD), Scores per subscale range from 0 to 21, with higher scores indicating psychiatric distress. (Goldberg & Hillier, 1979; Koeter and Ormel, 1991).

*Individual approach (IA-VAS and HRQoL mark)*
All patients were requested to state a domain of their life which they considered have the largest influence their health related quality of life the most, either in a positive or a negative way. The current value of this domain on the health related quality of life was rated on a Visual Analogue Scale (VAS), ranging from 0 (worst possible) to 100 (best possible). This is called the IA-VAS (individual approach visual analogue scale). Patients were also requested to rate their actual overall health related quality of life with a mark ranging from 0 to 10 (0 representing the worst and 10 the best quality of life imaginable), to which we will refer to as the HRQoL mark.

***Statistical analysis***
Descriptive statistics was used to summarize sample characteristics. Pearson's correlations were calculated between the (sub)scales of the SF-36, the MFIQ, the HADS, the GHQ, the IA-VAS and the HRQoL mark. Correlations were judged as low ($r<0.20$), moderate ($0.20 < r < 0.50$) or high ($r>0.50$) in accordance with Cohen's recommendations (Cohen, 1977). The level of significance was set at $p<0.05$. This study was approved by the Medical Ethical Committee of the UMCG.

## Results

*Patients' demographics and scores*

In total, 106 patients were approached to participate in the present study. Of these 106, 17 decided to withdraw resulting in 89 patients (84% response), all of Dutch origin, who were willing to participate (84 females and 5 males; mean age 41.0 years (sd 13.2 years). The median duration of pain in these patients was 6.5 yrs (range 1-35 years). According to the RDC/TMD, a group I (myofascial pain) diagnosis was established in 32.6% of all patients. A group II diagnosis (disc displacement) was made in 3.4%. A group III (arthralgia, osteoarthritis and osteoarthrosis) diagnosis was made in 36.0%. A combined group I and II diagnosis was made in 4.5%, combined group I and III in 16.9% and combined II and III diagnosis in 3.4%.

*Standardized approach*

The outcomes of the SF-36, FIRS, HADS and GHQ are listed in table 1. When applicable, the reference values are also listed.

*Individual approach*

The domains called at the answer of the open ended question were of major influence on their HRQoL could be categorised in the following seven domains: 1 health, 2 family/interpersonal relationships, 3 job/education, 4 social contacts other than family or spouse, 5 religion, 6 hobby/sport, and 7 other. The domain mentioned most frequently was *family/relation* (64.0 %). The domain *health* was mentioned in 19.1 % as being the most important. Domains mentioned less frequently were *job/education* as well as *hobby/sport* (2.2%) and religion (1.1 %). Domains allocated to the domain other were mentioned by 3.4% of the patients. Items mentioned allocated to this domain were independence and love. The average IA-VAS was 93.9 (sd 13.8) and the average HRQoL mark 71.3 (sd 13.3).

*Correlation with the individual domains*

In order to assess the relationship between domains measured in the standardized fashion and the domains called the open ended question, correlations were calculated between scores on the (sub)scales of the SF-36, MFIQ, HADS and GHQ and the ratings of the most frequently called domains *health* and *family/relation*. None of the SF-36, MFIQ, GHQ and HADS (sub)scales correlations were significantly correlated with the IA-VAS of domains health and family/relation. Table 2 shows that all correlations between the overall HRQoL (HRQoL mark) and the standardized measures (SF-36, MFIQ, GHQ and HADS) were statistically significant. The correlations of the HRQoL mark with the SF-36 ranged from .290 to .460, indicating a moderate (positive) relationship. The correlations of the HRQoL mark with the FIRS, GHQ and HADS ranged from -.245 to -.516, indicating a moderate to high (negative) relationship.

Table 1. SF-36, MFIQ, HADS and GHQ scores

| Scale | Reference (SD) | Mean (SD) |
|---|---|---|
| SF-36 PF | 83.0 (22.8) | 74.3 (26.6) |
| SF-36 RP | 76.4 (36.3) | 49.3 (40.9) |
| SF-36 BP | 74.9 (23.4) | 52.0 (22.6) |
| SF-36 GH | 70.7 (20.7) | 55.9 (20.0) |
| SF-36 VT | 68.8 (19.3) | 54.5 (19.6) |
| SF-36 SF | 84.0 (22.4) | 68.3 (24.6) |
| SF-36 RE | 82.3 (32.9) | 82.0 (37.5) |
| SF-36 MH | 76.8 (17.4) | 71.0 (16.6) |

**Used abbreviations (for questionnaire properties see text)**

SD: standard deviation
SF-36: The Short Form Health Survey,
PF: physical functioning;
RP: role limitations physical;
BP: bodily pain;
GH: general health;
VT: vitality;
SF: social functioning;
RE: role limitations emotional;
MH: mental health;

| Scale | Reference (SD) | Mean (SD) |
|---|---|---|
| FIRS | n/a | 3.1 (1.7) |
| HADS-A | n/a | 5.0 (3.6) |
| HADS-D | n/a | 3.8 (3.4) |
| GHQA | 7.5 (4.0) | 6.2 |
| GHQB | 5.9 (4.2) | 5.8 |
| GHQC | 8.0 (2.6) | 7.0 |
| GHQD | 1.8 (3.0) | 1.6 |

FIRS,: function impairment ration scale;
n/a: not available
HADS-A: Hospital Anxiety and Depression Score Anxiety;
HADS-D: Hospital Anxiety and Depression Score Depression.
GHQ: General health Questionnaire
GHQA: somatic symptoms;
GHQB: anxiety and insomnia;
GHQC: social dysfunction;
GHQD: severe depression;

Table 2. Pearson Correlation Coefficients of HRQoL mark with SF-36, FIRS, HADS and GHQ

| | HRQoL mark | |
|---|---|---|
| | PCC | p-value |
| SF-36 PF | .303 | .009 |
| SF-36 RP | .460 | .000 |
| SF-36 BP | .441 | .000 |
| SF-36 GH | .431 | .000 |
| SF-36 VT | .406 | .000 |
| SF-36 SF | .470 | .000 |
| SF-36 RE | .290 | .013 |
| SF-36 MH | .400 | .000 |

**Used abbreviations (for questionnaire properties see text)**

SD,: standard deviation
SF-36: The Short Form Health Survey,
PF: physical functioning;
RP: Role limitations physical;
BP: bodily pain;
GH: general health;
VT: vitality;
SF: social functioning;
RE: role limitations emotional;
MH: mental health;

| | HRQoL mark | |
|---|---|---|
| | PCC | p-value |
| FIRS | -.291 | .010 |
| HADS-A | -.322 | .004 |
| HADS-D | -.516 | .000 |
| GHQA | -.372 | .01 |
| GHQB | -.245 | .025 |
| GHQC | -.422 | .000 |
| GHQD | -.277 | .011 |

FIRS: function impairment rating scale;
HADS-A: Hospital Anxiety and Depression Score Anxiety;
HADS-D: Hospital Anxiety and Depression Score Depression.
GHQ: General health Questionnaire;
GHQA: somatic symptoms;
GHQB: anxiety and insomnia;
GHQC: social dysfunction;
GHQD: severe depression;

## Discussion

In this study we explored whether the individualized approach reveals corresponding or other information compared to the information obtained from standardized measurements of psychosocial functioning and HRQOL in orofacial pain patients. These patients may, apart from or due to pain and physical (mandibular) impairment, suffer from psychological and psychosocial problems that may influence their HRQoL. As HRQoL is a multidimensional construct, we decided not to include purely QoL assessment tool (SF-36) but also questionnaires which cover dimensions of QoL. So physical and psychological dimensions, including anxiety and depression were assessed separately. In order to get a complete picture, the results obtained from the individualized and standardized approaches were compared.

Our results showed that when patients were asked to mention domains that influence their HRQoL, the domain *family/relation* was mentioned most frequently. However, this domain was not explicitly taken into consideration at the standardized approach. Against our expectations, the domain *health* was only mentioned by 19.1 % of the patients as the most important domain. In the standardized approach, this domain, however, is often included by most of the instruments. As could be expected, in patients who mentioned *health* as the most important domain, the VAS score (IA-VAS) given to this domain was found to be significantly correlated with the SF-36 subscale *mental health*. On the other hand, the domain health was not significantly correlated with scores on the FIRS, the SF-36 subscales *general health, pain, vitality* or the GHQA (somatic) subscale.

Similarly, when patients depict social contacts as an important domain in their HRQoL, one would expect that this would be reflected in the scores on the social dimensions of the standardized instruments. This discrepancy between the outcomes of the individually judged most important domains (in our study *health* and *social contacts*) and the subsequent judgement of similar domains on standardized questionnaires imply that different approaches serve different purposes and do actually measure different things. An explanation for this finding may be that, according to the patient, not all items used in the standardized questionnaires appeared to be related to the corresponding domain being mentioned as most important. A concern in this part may be the categorization of the named domains into seven predefined domains, as it may be susceptible to subjectivity. However, the domains mentioned were in large agreement with the mostly predefined domains, and there was a high agreement in selection of words. We therefore argue that this subjectivity can be ignored in the interpretation of the results.

Furthermore, our results showed that the HRQoL mark was significantly correlated with the outcomes of the standardized questionnaires (SF-36, MFIQ, HADS and GHQ). These correlations may support the idea that in a screening or clinical setting, the overall rating of the patient's HRQoL mark provides a representative impression of the patient's HRQoL. Correlations of the HRQoL mark with the SF-36 were moderate, implying convergent validity. In addition when the HRQoL mark was compared with different

dimensions of QoL, the correlations were found to be moderately to high (negatively) correlated, also implying convergent validity. This finding is in line with earlier findings of De Boer and co-workers (2004). They used a VAS to record the overall HRQoL and found that the VAS was a valid and reliable method for measuring the global HRQoL. (De Boer et al., 2004).

It should be emphasized that the individual approach has been introduced to explore possible agreements with standardized approaches. This has not (yet) been studied for its validity and reliability. However, the QoL mark shows a correlation with all the SF-36 items, indicating a convergent valid measure.

In conclusion, our explorative study showed that when patients were asked about their HRQoL in a structured, but open manner, they can and may report new, unknown facts or information, which has not been clarified in the history taking or in standardized assessment. In addition, a short, individual approach of HRQoL provides insight in the patients' perception of the environment and provides extra information complementary to standardized methods, which may provoke further, thorough psychological assessment.

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# General discussion

# 5

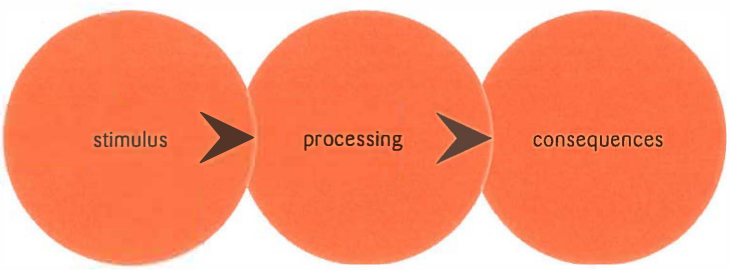
## General discussion

Pain is, by definition, an individual experience and is associated with tissue damage. However, somatic lesions usually are far less obvious in chronic pain than in acute pain conditions, and in many chronic pain cases a somatic lesion may not even exist any more at the time of examination. On the other hand, psychosocial factors play a major role in chronic pain conditions. As a consequence, diagnostic assessment in chronic pain is difficult and complex.

Traditionally, diagnostic pain assessment is performed based on the assumption that tissue damage (somatic origin) causes the pain and therefore, the focus should be on the search for this tissue damage (Feinmann, 2004). In essentialism, diseases are considered to be causal for illness. Therefore, the clinician is focused on identifying the disease and providing treatment. Still, from this point of view, clinicians and patients search for a biomedical explanation for the pain. When this explanation cannot be found, patients will undergo additional tests and even treatments, ever aiming at the identification of a somatic cause. When this fails, patients are frequently thought to be malingering or the pain is considered psychic in origin.

More recently, the influence of psychosocial factors on the persistence of both acute and chronic pain have been widely acknowledged and incorporated in the diagnostic assessment. However, this does not imply that chronic pain conditions are psychological or psychiatric in nature, which should be approached accordingly. Nevertheless, both the medical model and the psychosocial model focus on causal explanations. In analogy to the essentialists' hunting for the causation of illness, such an approach harbours some flaws as the etiology of many diseases remain of unknown origin, known causes are of diverse types, and causation can be intricate and involve interaction with other factors (Scadding, 1996). In such cases, an approach is preferred which recognizes these flaws and eventually aims at treatment of the patient with the disease rather than treatment of the disease. "Nominalists definitions do not attempt the impossible task of revealing the essence of the *definiendum*, but state how words or other symbols are to be related to observable phenomena" (Scadding, 1988).

We have proposed an approach in which the focus is on one or more Stimulus-Processing-Consequences (SPC) levels, to enhance and enrich the diagnostic assessment in chronic orofacial pain.

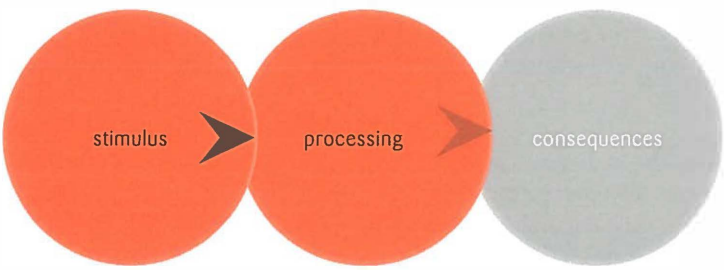


*Current research in orofacial pain*

After assessing existing studies on diagnostic tests in orofacial pain, using a minimum set of criteria including the presentation of selection criteria, randomization and blinding, it became clear that:

- only cases of well defined orofacial pain types have been studied properly.
- only a minority of all diagnostic research seems to be of sufficient quality.

This implies two main issues in current pain research. First, patients with orofacial pain with clinical presentation, suiting a diagnosis in a current classification system may relatively easily be included in clinical research, as inclusion criteria (i.e. diagnostic criteria) are relatively obvious. In orofacial pains in which causes are more obscure, this will be more difficult. So the challenge in diagnostic test development remains for the less obvious, mainly chronic idiopathic orofacial pains. Secondly, if diagnostic tests as such are studied, the trial should be well designed, thereby enhancing the quality and value of the assessment, diagnosis and treatment of chronic orofacial pain. The purpose of conducting diagnostic research in this context is the development of valid diagnostic tests. Therefore, a minimum of criteria should be obeyed to draw firm conclusions based on the research's results. The results from our review (chapter 2) signify the importance of using standard quality measures in conducting studies, and the consequences of proper reporting of the applied quality measures in research papers. It could well be that in some studies most criteria were fulfilled, but not reported. Although seemingly disappointing, it should function as an encouragement for future research(ers) in order to enhance the quality and relevance of their diagnostic research in chronic orofacial pain.




*Pharmacodiagnostics*

When focusing on the stimulus and processing levels, pharmacodiagnostic methods are potentially valuable. Locally acting pharmcodiagnostics could be of help in locating the structure from which the pain emanates from i.e. the source of pain. Together with careful history taking, the source of pain may be established by using clinical tests aimed at provocation of pain or using diagnostic anesthesia aimed at eliminating the pain response. In acute pain, e.g. when pulpitis is suspected (characterized by its poor localizability), this is done to locate the painful tooth. In the assessment and treatment of chronic orofacial pain conditions, diagnostic anesthesia can also be helpful. In one type of orofacial pains, temporomandibular disorders (TMD), anesthesia may be used to specify the origin of the pain, i.e. to find out whether the pain is of articular origin or not.

This is especially important when it has far-reaching consequences (e.g. as indication for invasive c.q. surgical treatment). We showed that injection of anesthesia in the temporomandibular joint (TMJ) causes more pain relief than placebo injection. However, the anesthesia did not completely diminish the pain in all cases, which may be due to the involvement of nearby structures, for instance in the case of temporomandibular disorders with both articular and muscular involvement or compensation. The (in)complete pain diminishing effect may also be due to anatomical, physiological or psychological factors in individuals, such as the duration of pain experience, the reproducibility of the anesthesia technique, the (in)ability to use of a standardized dosage in each patient, the coping strategies of the individual and the anticipation on the effects of the administered drug. These factors must be constantly kept in mind when using this diagnostic test. Therefore, to rule out the possibility of a false positive response, repeated anesthetic injections and the use of placebo injections may give indications of the reliability of the response. This is especially advisable when the injection suggests an intra-articular origin of pain implying the need for further irrevocable treatment. Alternatively, to confirm an articular origin, anesthesia of the nervus auriculotemporalis could be considered, although it is not completely responsible for innervation of the TMJ (Donlon et al, 1984).

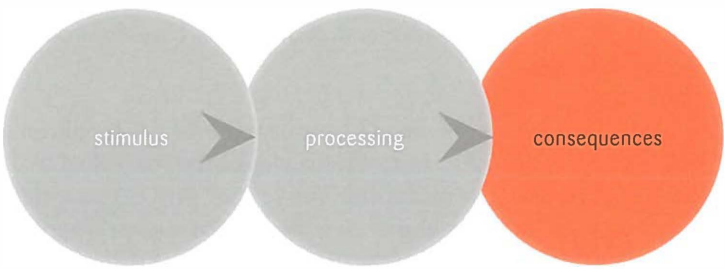
In addition to local pharmacodiagnostics, systemic pharmacodiagnostics make use of the response of patients to different pharmacological agents. In a first attempt to study whether a pharmacodiagnostic test could be an aid in disentangling chronic pain patients, early findings revealed that this test was well tolerated, and that in nearly one third of the patients tested, a classification of the underlying pain mechanism could be based on the response to the test. Although classification of only one third of patients may seem disappointing, one must take the patient population into consideration: all patients had chronic pain that could not be diagnosed based on history, clinical and additional (e.g. imaging) information.

Against this background, the ability to classify a third of these patients is useful and a step in the right direction. Moreover, the ability to classify patients based on a pharmacodiagnostic test was in turn dependent on the effects of fixed low-dose amounts of pharmacological agents in a heterogeneous patient sample. Therefore, the value of the classification of the test needed to be validated.

Nociceptive, neuropathic, and sympathetically maintained pain (SMP) are currently considered to be the three main pain mechanisms. Therefore, three distinct groups of patients (with nociceptive, neuropathic, and SMP) were selected and underwent a slightly simplified version of the test, i.e. without thiopental. In the validation study, the pharmacological test seemed to be able to differentiate between the three different pain categories. However, it was not possible to determine one or more test components that could truly identify a single mechanism (or a combined pattern of mechanisms). A multi-level analysis was used, as it respects the dependency of the different drug deliveries (and different Visual Analogue Scale scores) within one patient at one level, and the patient groups c.q. the pain groups at a second level. Our study was performed in patients whose

diagnoses were based on clinical characteristics; it is possible that in some of these patients multiple pain mechanisms were present. This could be an explanation why not all patients within each group responded similarly. Nevertheless, throughout the course of the test, the test could differentiate between the three pain groups. It would be desirable to be able to use this test in patients with pain of unknown mechanisms. In these patients, the pain may be the result of a combination of the different mechanisms, with one of these mechanisms playing the major role. When the test is applied to those patients, the (major) pain mechanisms may be elucidated. In order to draw firm conclusions, future research should focus on enhancing the test, and the clinical implications of test outcomes, i.e. basing and evaluating treatment on test outcomes.

The performance of the test may be (further) enhanced by using specific pharmacological agents and adapting the applied dosages to the individual's response. As clearly studied and reported, pain chronicity involves a variety of neuroplastic changes which may also affect the responses to these agents. Somatosensory phenomena such as hyperalgesia, hypesthesia and dysesthesia were not taken into account in test responses. But even when neuroplastic changes have occurred, testing patients may be of help in determining an absence of peripheral mechanisms and thus excluding possible peripheral treatment. When a pharmacological test is used in an early stage, peripheral mechanisms may still be active.




*Quality of Life*

When focusing on the consequences of pain, the results of our quality of life (QoL) studies show that when temporomandibular pain lasts longer, quality of life becomes more affected. This has been assumed in temporomandibular disorders, but evidence was scarce. When dividing patient population in three groups according to duration of pain, and also when taking the pain duration as a continuous variable, it becomes obvious that there is a difference between groups of different pain duration concerning physical and social functioning. Although outcomes may meet the expectations, this study confirms what has been previously assumed. Accordingly, treatment strategies can be based on these findings, paying more attention to social factors in patients with pain lasting for a longer period of time.

Although not yet studied for validity and reliability, asking patients to rate one domain that is of influence on their quality of life and asking them to rate their QoL using a mark provides a quick indication and may serve as point of departure for further investigations.

When a low QoL is scored, further elucidation by more detailed questions and questions addressing the major determinant of the low score are indicated. A recent study showed that the impact of the TMD on the QoL was related to the type of TMD (Barros V de et al, 2009). As shown in our previous study: the longer pain problems last, the more pronounced the effects on the QoL. So especially in these patients, using a brief indicator is recommended, giving attention to and recognition of the psychosocial consequences which, together with assessment of other levels of the pain, has a synergistic effect.

## Future perspectives

Current and future research on orofacial pain takes place at different levels. Focusing solely on one level may lead to inadequate pain management, as different levels of pain are involved.

In the development of pharmacodiagnostics, an individually tailored set-up should be developed and investigated to improve the distinguishing capacity. The value of using pharmacodiagnostics in predicting treatment outcome should also be studied. Although this strategy focuses mainly on the somatic aspect it could, in combination with psychological assessment, contribute to proper assessment and treatment of chronic orofacial pain patients.

Evidence for the use of new or current assessment and treatment modalities for chronic pain patients should be established more firmly. In randomized, placebo controlled trials evaluation of currently used (and seemingly successful, but yet not proven) treatment should be done. Difficulties in generalizability of patient cohorts with unclear diagnosis may be overcome by the development of a new classification system which differentiates alternative and redefined current rationales.

Further development and extension of knowledge should take place at a basic science level, i.e. molecular processes, genetic variability and "susceptibility" of chronic pain patients. In search of etiological factors and treatment modalities for chronic pain, the transition of acute pain into chronic pain deserves broad attention. When the factors are identified that enable the pain to persist, chronic pain may be prevented.

*It is not your duty to complete the work, but neither are you free to desist from it.*
*(Avot 2:15)*

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# Summary

# 6

## Summary

Orofacial pain is a common reason for a patient to visit the physician or dentist. In most cases, diagnosis will be relatively straightforward and an adequate treatment can usually be provided. When pain persists over time (i.e., when pain becomes chronic), this will hamper the diagnostic process by so called neuroplastic changes of the nervous system. Because of these physiological and biochemical changes, a normally non-painful stimulus may be perceived as painful. Neuroplastic changes may also explain the phenomenon of referred pain, i.e. pain is perceived in an area that is different from the source from where it originates. Moreover, chronicity leads to an increased involvement of psychosocial factors in the perception and experience of pain, which further complicates the problem. To diagnose pain, different classification systems have been developed. In these classifications, the pain conditions are usually described in terms of symptomatology. When the clinical presentation of symptoms becomes less clear, e.g. because of changes related to chronicity, classification will be more difficult. This will eventually have consequences for pain management. Especially for this patient group, there is a need for additional diagnostic information which may clarify the clinical picture. The aim of this thesis is to enhance the diagnostic assessment of chronic orofacial pain.

Irrespective of the complexity of the pain, it will essentially originate from actual or former tissue damage. This stimulus is subsequently processed within the nervous system and will eventually give rise to certain responses, i.e. pain experience and behavior (consequences). Thus, in the pain process essentially three components are involved: stimulus, processing and consequences. We therefore introduce the stimulus-processing-consequences (SPC) model as a starting point for the assessment of pain.

In most patients pain with acute pain, tissue damage plays a major role, while the processing of the stimuli is unaffected. Therefore, diagnosis and treatment of these patients will mainly focus on the stimulus. In patients with chronic pain, tissue damage will play a less dominant role and the consequences will largely be accompanied by changes in the processing of the stimuli. In this group, it is therefore important to not solely focus on the stimulus (the origin and extent of tissue damage), but to include explicitly the processing of the stimulus and its consequences in the diagnostic assessment.

In order to study the (quality of) current diagnostic methods and their applicability in patients with persistent orofacial pain, the results of a systematic review are presented in chapter 2. The systematic review was conducted with specific search terms for clinical studies in orofacial pain. Because it concerned diagnostic research, a methodological filter aiming at diagnostic research was applied.
The search retrieved 1047 articles. Of these articles, the titles and abstracts were screened for relevance. In order to obtain qualitatively adequate studies, eventually 72 studies were assessed using the Quality Assessment of Diagnostic Accuracy Studies list (QUADAS). This checklist consists of 14 items that refer to internal validity. We argued that studies scoring "yes" in more than half of the questions could be included for further appraisal.

This resulted in 15 qualitatively adequate studies. Of these studies, eight investigated the diagnostic value of magnetic resonance angiography for vascular compression in trigeminal neuralgia. Three studies reported the diagnostic value of magnetic resonance imaging in the temporomandibular joint (TMJ) arthralgia. The others studied a bite test for identifying muscular or articular origin of pain in the TMJ region, neurophysiological tests for the assessment of facial nerve deficits, the diagnostic validity of pain complaints and symptoms and pulpal tests in patients with pulpal problems, diagnostic anesthesia in intra-articular temporomandibular joint pain. This review demonstrates that when studies on diagnostic tests in orofacial pain conditions are reviewed, only a minority remains. Moreover, these studies predominantly aim at well-defined orofacial pain types, which are relatively well described and easy to diagnose. There is a large need for diagnostic methods aiming at (more) complex pain conditions, such as chronic orofacial pain.

Chapter 3 aims at farmacodiagnostics: diagnostics using pharmacological agents. This focuses mainly on the stimulus (chapter 3.1) and the processing of the information within the nervous system (chapter 3.2 and 3.3).

In chapter 3.1 a study is described in patients experiencing pain in the TMJ area. In these patients it is important to establish whether the pain originates from the joint proper. In the diagnostic process, intra-articular anesthesia has frequently been used. In this research, the distinguishing capacity of intra-articular injection of anesthesia compared to a placebo is studied. In a double-blind placebo controlled cross-over trial, 19 patients who were clinically diagnosed with TMJ pain (arthralgia) were studied. Patients received both placebo and anesthesia injections, with a two weeks wash-out period between the injections. A computer program determined the order of the injections (randomization). Both placebo and anesthesia were delivered in identical carpules by the hospital pharmacy, in order to be sure that both the patients and the clinician were unaware of the injected substance (double-blinded). At the end of the study, the randomization code was broken. The anesthesia had a pain diminishing effect, measured on a Visual Analogue Scale (VAS, of 100 mm) of 12.8 mm (SD 23.5) compared to a pain increasing effect of the placebo of 4.5 mm (SD 15.0). This difference was statistically significant. It seems that intra-articular anesthesia can be used as a diagnostic tool in these patients. However, it should be noted that there is always a chance that patients respond false positively to an injection and the injection should therefore be repeated, in order to verify the results. The results of an intra-articular injection should be interpreted with caution, especially when the results have far-reaching consequences, e.g. surgery.

In chapter 3.2 the results of a retrospective study in 46 patients with chronic orofacial pain, undergoing a pharmacodiagnostic test (PDT), are described. In none of these patients, the history taking and standard clinical and radiographic examination revealed a proper diagnosis and treatment strategy. During the PDT, different pharmacological agents are subsequently delivered intravenously in a specific order. These agents are directed to specific pain mechanisms. The test consisted of fentanyl and its antagonist naloxone (aiming at nociceptive pain), thiopental (aiming at central pain), phentolamine

(aiming at sympathetically maintained pain) and lidocain (aiming at neuropathic pain). These infusions were interchanged with placebo. Before the test and after each delivery the patients were asked to rate their pain on a VAS. When the VAS score decreased at least 33% compared to the baseline, the patients was classified as "responder".

Out of 46 patients, eventually 16 could be classified as a responder to one or more of the pharmacological agents. The results of this study suggest that the pharmacodiagnostic test may offer valuable diagnostic information, especially in a patient group like this, where there is a need for additional information.

To obtain more information regarding the value of this test, validation is required. The results of the study on this topic are described in chapter 3.3. In this trial, three groups underwent the pharmacodiagnostic test.

- A group with nociceptive pain (a day after the extraction of their third molar)
- Patients with neuropathic pain (from the Department of Neurology or Pain Center diagnosed with a mono- or poly neuropathy)
- A group with sympathetically maintained pain (patients with the chronic regional pain syndrome and patients with a pain diminishing effect of a sympathicolytic procedure)

Multilevel analysis, performed to correct for the effect of the subsequent infused agents in different patients in three pain groups, revealed that the pharmacodiagnostic test was capable of differentiating between the three pain groups. However, univocal classification of an individual patient, based on the response on one or more parts of the tests, was not yet possible. The test should be further developed and modified, for instance by using individual dosages based on body weight or by titrating on effect.

Focusing on the consequences of the pain, chapter 4 aims at 'quality of life' (QoL). It is generally assumed that QoL (a concept incorporating different aspects of physical and psychological health and social functioning) is an individual concept, which is affected by the duration of pain. In patients with temporomandibular disorders (TMD) this is also assumed, although not extensively studied.

In the study described in chapter 4.1 the influence of the duration of pain on the QoL was determined in 95 patients with a TMD. Different questionnaires assessing different aspects of quality of life were used in these patients. Patients were divided into three groups based on the duration of pain: one group with pain present less than 1 year, one group with pain present between 1 and 3 years and one group with pain more than 3 years. Patients with pain which was present less than 1 year scored 'worse' than scores retrieved from a reference population. A significant correlation was found between physical functioning and mandibular impairment on one hand and pain duration on the other hand. It seemed that mental health was not, but social functioning was affected with a longer pain duration. These findings cannot be neglected and should therefore be incorporated in the assessment (diagnosis) as well as in the management of these patients.

Whether the assessment of quality of life can be limited to standardized questionnaires or an individualized approach has additional value is described in chapter 4.2. Besides using standardized QoL instruments and health questionnaires, 89 patients with a TMD were asked to indicate and rate a domain that most influenced their health related quality of life (HRQoL) and to rate their overall HRQoL with a mark ranging from 0 to 10. When patients were asked to depict a domain that influences their HRQoL, the domains health and family were indicated most frequently. This could not be retrieved using the current standardized instruments. Furthermore, all correlations between the HRQoL mark and the standardized measures appeared to be statistically significant. This study shows that an individual approach of HRQoL may provide a relatively quick insight into the patients' perception of the environment and provides extra information concerning domains determining (TMD) patients' quality of life. This may be a valuable starting point for further (psychological) diagnostic assessment.

The discussion in chapter 5 reveals that pharmacodiagnosis serves a role in the process of enhancing the diagnostic armamentarium in chronic orofacial pain. The pharmacodiagnostic test seems to be able to differentiate between patients with pain different pain mechanisms that may also play a role in orofacial pain. Further enhancement of the test should take place, however, for instance by using individual dosages. The effect of treatment could also be correlated to a specific test outcome. Besides this, the quality of life should be incorporated in the assessment of chronic pain patients. When pain persists, the quality of life will be negatively affected. The necessity of additional diagnostic assessment and important domains of quality of life can be determined using simple questions.

By involving different SPC levels simultaneously in pain diagnosis and by developing specific instruments for each of these levels, a synergistic effect on the efficacy of diagnostics and eventual management of chronic orofacial pain may be accomplished.

## Samenvatting

Pijn in de mond en het gebied van het aangezicht (orofaciale pijn) is een belangrijke reden voor een patiënt om naar een tandarts of arts te gaan. In de meeste gevallen zal de diagnostiek relatief eenvoudig zijn en zal er snel een adequate behandeling ingezet kunnen worden. Indien de pijn langer aanwezig is (chronisch wordt), wordt de diagnostiek vaak bemoeilijkt door zogenaamde de effecten van neuroplastische veranderingen van het zenuwstelsel. Door deze veranderingen in fysiologie en biochemie kunnen gewoonlijk niet-pijnlijke prikkels nu wel als pijnlijk worden ervaren. Neuroplastische veranderingen kunnen er ook toe leiden dat pijn op een andere plaats wordt gevoeld dan waar deze zijn oorsprong heeft (gerefereerde pijn). Chroniciteit leidt er ook toe dat psychosociale factoren een grotere rol gaan spelen bij de ervaring en beleving van de pijn, hetgeen het beeld vaak mede compliceert.

Om pijn te diagnosticeren zijn diverse classificatiesystemen ontworpen. De beelden hierin zijn in de regel gedefinieerd op basis van de symptomatologie. Naarmate de klinische presentatie van symptomen minder eenduidig wordt door de veranderingen die optreden als gevolg van chroniciteit, zal classificatie lastiger zijn. Dit zal uiteindelijk ook consequenties hebben voor de behandeling. Bij deze patiënten is er een grote behoefte aan aanvullende informatie, die de klinische situatie kan verhelderen. Het doel van dit proefschrift is de mogelijkheden voor de beoordeling van chronische orofaciale pijn te vergroten.

Hoe gecompliceerd pijn ook is, in essentie vindt deze zijn oorspong in actuele of vroegere weefselschade. Deze vormt een stimulus, die vervolgens in het zenuwstelsel wordt verwerkt, hetgeen uiteindelijk aanleiding geeft tot bepaalde reacties, ervaringen en gedragingen (consequenties). Bij het pijnproces zijn dus drie componenten betrokken: stimulus, verwerking en consequentie. Wij introduceren daarom het stimulus-processing-consequences (SPC) model als basis voor het beoordelen van pijn.

Bij de meeste pijnpatiënten speelt de weefselschade een hoofdrol en verloopt de verwerking van de prikkels ongestoord; diagnostiek en behandeling zullen zich bij deze patiënten dan ook vooral op de stimulus richten. Bij patiënten met chronische pijn speelt de weefselschade doorgaans een minder dominante rol en lijken de consequenties grotendeels samen te hangen met veranderingen in de verwerking van de prikkels. Bij deze groep is het daarom van belang de diagnostiek niet uitsluitend te richten op de stimulus (de aard en omvang van weefselschade), maar hierbij de verwerking van prikkels en de consequenties nadrukkelijk te betrekken.

Om een overzicht te krijgen van de huidige stand van zaken van (de kwaliteit van) het diagnostisch onderzoek bij orofaciale pijnen worden in hoofdstuk 2 de resultaten van een systematisch literatuuronderzoek weergegeven. Het literatuuroverzicht werd verricht met specifieke zoektermen voor klinische studies naar orofaciale pijn. Aangezien er werd gezocht naar diagnostisch onderzoek is hier een methodologisch filter voor gebruikt.

De zoekacties leverden 1047 artikelen op. Van deze artikelen werden de titels en samenvattingen onderzocht op relevantie. Om onderzoek te verkrijgen dat kwalitatief voldoende was, zijn 72 relevante artikelen beoordeeld met behulp van de Quality Assessment of Diagnostic Accuracy Studies (QUADAS) lijst. Deze lijst bevat 14 onderdelen over interne validiteit. Wij achtten studies van voldoende kwaliteit als de artikelen aan minstens de helft van de 14 onderdelen voldeden. Dit resulteerde in 15 diagnostische studies van voldoende kwalitatief. Acht hiervan gingen over de beoordeling van trigeminusneuralgie met behulp van magnetische resonantie angiografie. Drie studies onderzochten de waarde van beeldvorming met magnestische resonatie bij artralgie van het kaakgewricht. De overige studies onderzochten een bijttest voor de oorsprong van kaakgewrichtspijn, een zenuwgevoeligheidstest bij aandoeningen van zenuwen in het aangezicht, de relatieve diagnostische waarde van pijnklachten, symptomen en pulpatests bij patiënten met pulpaproblemen en het gebruik van lokale anesthesie bij de diagnostiek van kaakgewrichtspijn. Dit literatuuronderzoek illustreert dat er slechts een beperkte hoeveelheid kwalitatief adequaat onderzoek op het gebied van de diagnostiek van orofaciale pijn voorhanden is. Opvallend is dat deze studies veelal zijn gericht op vormen van orofaciale pijn die relatief goed omschreven en eenvoudig te diagnosticeren zijn. Aan onderzoek naar diagnostische methoden gericht op complexe(re) vormen van orofaciale pijn (bijvoorbeeld chronische orofaciale pijn) is dringend behoefte.

Hoofdstuk 3 is gericht op de farmacodiagnostiek: diagnostiek met behulp van medicamenten. Deze richt zich met name op de stimulus (hoofdstuk 3.1) en beïnvloeding van de verwerking (processing) van prikkels (hoofdstukken 3.2 en 3.3).
In hoofdstuk 3.1 wordt een onderzoek beschreven bij patiënten die pijn ervaren in het gebied van het kaakgewricht. Bij deze patiënten is het van belang vast te stellen of de pijn zijn oorsprong heeft in het gewricht zelf. Hiertoe wordt in de diagnostiek wel gebruik gemaakt van intra-articulaire lokale anesthesie. In dit onderzoek wordt het onderscheidend vermogen van intra-articulaire injectie van een lokaal anesthesticum ten opzichte van een placebo onderzocht. In een dubbelblinde cross-over opzet werden 19 patiënten, klinisch gediagnosticeerd met kaakgewrichtspijn (arthralgie), onderzocht. Patiënten kregen een injectie met zowel een lokaal anestheticum als een placebo, met een periode van twee weken tussen deze twee injecties. Door een computerprogramma werd de volgorde van injectie bepaald (randomisatie). Beide vloeistoffen werden door de ziekenhuisapotheek in identieke carpules geleverd, waardoor zowel de patiënt als de arts op het moment van injectie niet wisten welk middel werd toegediend (dubbelblind onderzoek). Aan het einde van de studie werd de randomisatie onthuld.

De lokale anesthesie had een pijnverminderend effect, zoals werd vastgesteld op een Visuele Analoge Schaal (VAS) van 100 mm, van 12.8 (SD 23.5) ten opzichte van een pijnverhogend effect van de placebo van 4.5 (SD 15.0). Dit verschil was statistisch significant. Het gebruik van intra-articulaire anesthesie lijkt dus gebruikt te kunnen worden als diagnostisch instrument bij deze patiënten. Wel moet worden opgemerkt dat de kans bestaat dat patiënten ten onrechte positief reageren op een toegediende injectie en dat wellicht herhaling van de injectie nodig is om de uitkomst te verifiëren. De resultaten van een

intra-articulaire injectie zullen dus voorzichtig moeten worden geïnterpreteerd, vooral als de uitslag verregaande consequenties (bijvoorbeeld een chirurgische ingreep) heeft.

In hoofdstuk 3.2 worden de resultaten weergeven van een retrospectief onderzoek bij 46 patiënten met chronische orofaciale pijn, die een farmacodiagnostische test (FDT) ondergingen. Bij geen van deze patiënten leidde de anamnese en het standaard klinisch onderzoek aangevuld met röntgenologische informatie tot een duidelijke diagnose en behandeling. Tijdens de FDT worden verschillende farmaca na elkaar en in een vaste volgorde intraveneus toegediend. De farmaca zijn gericht op verschillende pijnmechanismen. De test bestaat uit fentanyl met zijn antagonist naloxon (gericht op nociceptieve pijn), thiopental (gericht op centrale pijn), fentolamine (gericht op sympathisch gemedieerde pijn) en lidocaine (gericht op neuropathische pijn). Deze onderdelen worden afgewisseld met de toediening van fysiologisch zout. Voorafgaande aan de test en volgend op elke toediening wordt aan de patiënt gevraagd de pijn op een VAS weer te geven. Wanneer de VAS score na toediening van een stof met minstens 33% ten opzichte van de baseline veranderde, werd de patiënt met betrekking tot dit farmacon geclassificeerd als "responder".

Van de 46 patiënten konden uiteindelijke 16 patiënten worden geclassificeerd als "responder" op een of meer farmaca. De resultaten van deze studie suggereren dat de farmacodiagnotische test waardevolle informatie kan opleveren, gegeven de aard van de patiëntengroep, waarbij immers aanvullende diagnostische informatie welkom is.

Om over de waarde van de test extra informatie te verkrijgen, is het echter nodig om de test te valideren. De resultaten van het onderzoek hiernaar staan beschreven in hoofdstuk 3.3. In dit onderzoek ondergingen drie groepen pijnpatiënten de farmacodiagnostische test:

- een groep met nociceptieve pijn (een dag na verwijdering van een verstandskies)
- een groep met neuropathische pijn (vanuit de afdeling neurologie of het pijncentrum gediagnosticeerde patiënten met een mono- of polyneuropathie)
- een groep met sympatisch gemedieerde pijn (chronisch regionaal pijnsyndroom I en met pijnvermindering na een sympathicolytische procedure)

Na een multi-level analyse, uitgevoerd om de effecten van de na elkaar toegediende middelen in de verschillende patiënten in de drie groepen te bestuderen, bleek dat de farmacodiagnostiche test in staat is om de drie pijngroepen van elkaar te onderscheiden. Eenduidige classificatie van een individuele patiënt op basis van de respons op een of meerdere onderdelen van de test bleek echter nog niet mogelijk. Hiervoor zal verdere ontwikkeling en modificatie van de test plaats moeten vinden, waarbij te denken valt aan een individuele dosering gebaseerd op lichaamsgewicht of aan titratie op effect.

Met een focus op vooral de gevolgen (consequences) van pijn richt hoofdstuk 4 zich op de kwaliteit van leven. Over het algemeen wordt aangenomen dat de kwaliteit van leven (een concept dat verschillende componenten bevat, zoals fysieke en psychische gezondheid en sociale aspecten) een individueel concept is, dat onder meer wordt beïnvloed

door de duur van het bestaan van pijn. Ook bij patiënten met aandoeningen van het mandibulaire bewegingsapparaat wordt dit verondersteld, hoewel dit is niet uitvoerig onderzocht.

In het onderzoek dat beschreven is in hoofdstuk 4.1 werd de invloed van de duur van aanwezigheid van de pijn op de kwaliteit van leven bepaald bij 95 patiënten met een aandoeningen van het mandibulaire bewegingsapparaat. Bij deze patiënten werden verschillende vragenlijsten afgenomen die betrekking hebben op verschillende aspecten van de kwaliteit van leven. De patiënten werden verdeeld in drie groepen op basis van de duur van de aanwezigheid van de pijn: een groep met pijn die minder dan 1 jaar aanwezig was, een groep met pijn die tussen 1 en 3 jaar aanwezig was en een groep met pijn die langer dan 3 jaar bestond. Patiënten met pijn langer dan een jaar scoorden slechter dan een referentie populatie op zowel fysiek als sociaal functioneren. Ten aanzien van mentale items verschilden geen van de groepen met de referentie populatie. Er werd een significante correlatie gevonden tussen fysiek functioneren en mandibulaire beperking aan de ene kant en duur van de pijn aan de andere kant. Het lijkt er dus op dat de mentale gezondheid vrijwel niet wordt aangetast door een langere duur van pijn, maar dat het sociale functioneren wordt beïnvloed door langdurige aanwezigheid van pijn. Deze bevinding kan niet worden genegeerd en hieraan zal zowel bij de beoordeling (diagnostiek) alsook bij de behandeling van deze patiënten dan ook aandacht moeten worden besteed.

Of de beoordeling van de kwaliteit van leven het beste met gestandaardiseerde vragenlijsten kan worden uitgevoerd of dat een individuele benadering daarbij een meerwaarde heeft, wordt beschreven in hoofdstuk 4.2. Naast gestandaardiseerde kwaliteit van leven vragenlijsten en gezondheidsvragenlijsten werd er aan 89 patiënten met een aandoening van het mandibulaire bewegingsapparaat gevraagd om aan te geven wat het belangrijkste aspect is van hun kwaliteit van leven en hoe zij dit aspect persoonlijk waarderen. Ook werd aan deze patiënten gevraagd hun "overall" kwaliteit van leven te waarderen met een rapportcijfer (0-10). Deze patiënten gaven duidelijk aan dat "gezondheid" en "familie" belangrijke aspecten zijn die hun kwaliteit van leven bepalen. Dit kwam echter uit de gestandaardiseerde vragenlijsten niet naar voren. Verder bleek het gegeven rapportcijfer met alle onderzochte gestandaardiseerde items significant te correleren. Uit dit onderzoek blijkt dat een individuele benadering snel inzicht kan geven in de aspecten die door patiënten met een aandoening van het mandibulaire bewegingsapparaat als bepalend voor hun kwaliteit van leven worden ervaren. Dit geeft samen met een eenvoudige "overall" waardering van de kwaliteit van leven inzicht in de noodzaak van en een goede uitgangssituatie voor verder diagnostisch (psychologisch) onderzoek.

Uit de discussie in hoofdstuk 5 komt naar voren dat bij het vergroten van het diagnostische arsenaal bij orofaciale pijn een rol is weggelegd voor de farmacodiagnostiek. De farmacodiagnostische test lijkt onderscheid te kunnen maken tussen patiënten met verschillende pijnmechanismen die ook een rol spelen bij orofaciale pijn. Verdere verfijning van dit instrument dient echter plaats te vinden, onder meer door met geïndividualiseerde doseringen te werken. Ook zou het effect van een uitgevoerde behandeling kunnen

worden gecorreleerd aan een bepaalde testuitslag. Hiernaast zal de kwaliteit van leven moeten worden meegenomen bij de evaluatie van chronische pijnpatiënten. Naarmate pijn langer bestaat, zal de kwaliteit van leven nadelig worden beïnvloed. De noodzaak van verder onderzoek en de belangrijkste bijdragende aspecten van de kwaliteit van leven kunnen aan de hand van simpele vragen worden vastgesteld.

Door de verschillende SPC niveaus gezamenlijk bij de pijndiagnostiek te betrekken en op elk van deze niveau's gerichte instrumenten te ontwikkelen kan een synergistisch effect op de doelmatigheid van de diagnostiek en uiteindelijk de behandeling van chronische orofaciale pijnpatiënten worden bereikt.

## Dankwoord

Alhoewel ik soms het idee had alles alleen te moeten doen, heeft de voltooiing van dit proefschrift niet plaats kunnen vinden zonder de medewerking en steun van een groot aantal personen. In de ontwikkeling die ik in die periode heb doorgemaakt, zijn daarbij een aantal mensen tevens zeer inspirerend geweest. Vooraleer wil ik alle patiënten en proefpersonen bedanken die in de afzonderlijke onderdelen hun medewerking hebben verleend.

Prof. Dr. Stegenga. Beste Boudewijn, door contact met jou kwam ik terecht op de afdeling Kaakchirurgie. Hierdoor was mijn interesse in dit vak en onderzoek snel gewekt. Tijdens de gehele onderzoeksperiode heb je me dikwijls een zet(je) in de goede richting gegeven. Ik heb veel respect voor jouw analytische vaardigheden en de manier waarop je die probeert over te dragen. De meeste onderzoeksbesprekingen waren erg inspirerend, waarbij je blik soms genoeg was om mezelf verder te laten denken en tot oplossingen te komen. Het is dan ook onbegrijpelijk waarom Microsoft in Word in de spellingscontrole *tegengas* als alternatief voor jouw achternaam geeft. Door jouw voortvarendheid en kritische houding heeft deze moeilijke materie zich laten vangen in dit mooie boekje. Mijn waardering voor jou gaat verder dan alleen als onderzoeksbegeleider en ik beschouw je dan ook als een wijze man. Dank voor je inzet en vertrouwen, ik hoop dat we hierna samen nog meer mooie projecten kunnen aangaan. Ik ben blij dat je mijn eerste promotor bent.

Prof. dr. De Bont. Mede door u en ook uw voorganger prof. dr. Boering heeft de afdeling kaakchirurgie een grote traditie en reputatie in de orofaciale pijn en kaakgewrichtsstoornissen. Dank dat u mij de mogelijkheid hebt gegeven hierin onderzoek te doen, op een afdeling met fijne collega's. Uw adviezen hebben de manuscripten en ook mij scherper gemaakt.

Dr. Van Wijhe. Beste Marten, in het UMCG heb je blijk gegeven op een alternatieve manier naar chronische pijnpatiënten te kunnen kijken. De ontwikkeling van de test is daar een voorbeeld van. Laat de resultaten van ons onderzoek een stimulans te zijn om met deze ontwikkeling door te gaan ten faveure van de pijnpatiënten. Bedankt voor je adviezen en medewerking.

Dr. Huddleston Slater. Beste James, door jouw komst op o.a. de afdeling(en) is de continuering van de aandacht voor zowel de gnathologie als de epidemiologie, maar ook kritische denkwijze gewaarborgd. Ik ben blij dat je besloot mee te willen werken aan een aantal stukken en heb van je kritische houding en originaliteit geleerd. Dank voor je inzet en inbreng in mijn onderzoek.

Drs. Reinders. Beste Jan-Jaap, als buurman op de universiteit kwam je buurten met oprechte interesse, die mij steeds duidelijk werd door je zinvolle kritische en doordachte gedachten over o.a. mijn manuscripten. Grappig dat je van buurman mede-auteur werd, je visie heeft zeker mijn kwaliteit van leven vergroot!

Dr. Ten Vergert. Beste Els, je adviezen ook vanuit een niet vakinhoudelijk perspectief waren zeer verhelderend. Jammer genoeg heb je niet het hele promotietraject mee kunnen maken maar ik ben je dankbaar voor je bijdragen.

De leden van de beoordelingscommissie; prof.dr. De Laat, prof.dr. Huygen en prof.dr. Kuks wil ik graag bedanken voor de beoordeling van het manuscript.

Mijn collega's van de afdeling Kaakchirurgie op met name de derde verdieping en elders; bedankt voor de inspirerende, onzinnige, geïnteresseerde, opbeurende, relativerende gesprekken van de afgelopen tijd. Van de bezoeken aan de Society of Oral Physiology (Storekro) in Naantali en Dresden hebben ik in meerdere opzichten iets geleerd.

Mw. Dam. Beste Anne-Margreeth, jij hebt je ontfermd over de uitvoering en planning FDT's wat niet altijd een eenvoudige klus was. Toch is het gelukt. Bedankt voor je inzet!

Collega's van het pijncentrum bedankt voor jullie medewerking.

Prof. Dr. Abbas. Beste Frank, in wat ik dacht wat de laatste fase was van de vervaardiging van mijn manuscript kwam ik bij je voor een informatief gesprek over de parodontologie. Dat dit gesprek zo zou lopen als dat het liep had ik niet kunnen hopen. Mede door de vrijheid die ik kreeg in de laatste maanden heb ik dit manuscript kunnen afronden. Bedankt voor het vertrouwen en de gelegenheid die jij me biedt om me te bekwamen in de parodontologie.

Collega's van het Centrum voor Tandheelkunde en Mondzorgkunde, binnen als buiten de sectie Parodontologie, dank voor jullie belangstelling en enthousiasme.

Heleen bedankt voor je begeleiding tijdens de opleiding totnutoe en je interesse in mijn onderzoek en de gezelligheid (o.a. tijdens de chirurgie!).

Renske, collega, kamer/studie/lotgenoot; je was mijn docent toen ik begon aan de studie tandheelkunde en ik vind het leuk dat ik nu jou af en toe wat wijs kan maken.

Prof. Dr. Loos. Beste Bruno, allereerst dank dat je mij hebt aangenomen. Het afronden van mijn proefschrift was daarbij een vereiste en ligt nu voor je. Dank voor je vertrouwen.

Prof. Dr. Van der Velden. Beste Ubele, in 2008 begon ik met de opleiding tot parodontoloog, waarbij ik sindsdien onder de indruk ben van je enthousiasme voor het vak en je drang naar kennis over elke uithoek van de parodontologie. Dit werkt inspirerend en heeft zelfs in dit boekje in ieder geval al z'n effect gehad. Wie weet wat volgt.

Al mijn andere "leermeesters" en collega's op het ACTA, in het bijzonder (in willekeurige volgorde) Wouter S, Tiddo, Ingrid, Fridus, Moniek, Spiros, Guido, Sergio, Dagmar, Fabiano, Yossi, Wouter v W, Elena, Wijnand. Bedankt voor jullie interesse voor het onderzoek gaandeweg de opleiding en natuurlijk jullie wijsheid!

Fam. Prins, beste Luuk en Hennie. Luuk, jij hebt mij zowel als tandarts en daarmee automatisch als mens opgevoed. Als ik bij mijn eerste waarneming niet bij jullie terecht kon gekomen, was ik niet wie ik nu ben. En daar heb ik geen spijt van gehad. Ik had me geen betere eerste waarneming kunnen wensen.

Beste Wouter, het was toeval dat jij mijn jaargenoot werd in de opleiding, maar ik vind het bijzonder dat dit redelijk snel tot vriendschap heeft geleid, waarbij je nuchtere karakter een relativerende werking op mij heeft gehad. Dank voor jouw en Erin's gastvrijheid tijdens verschillende verblijven in Amsterdam. Ik vind het bijzonder dat je mijn paranimf wilt zijn.

Beste Ger, lieve Ger. Al vanaf de basisschool was je de olijke (immer vriendelijke) krullebol. In onze studietijd is de vriendschap geïntensiveerd doordat je "bij ons" kwam wonen. Sindsdien hebben we veel contact, met een plezierige afwisseling tussen enorm kazen, kolder en jolijt en serieuze gesprekken. Ook heb ik de afgelopen jaren lange tijd van je onuitputtelijke gastvrijheid gebruik mogen maken. Ik hoop en ga er van uit dat we onze vriendschap in de toekomst voort zetten. Bedankt mijn paranimf wilt zijn.

Lieve vrienden; door jullie vriendschap alsook interesse heb ik het vol kunnen houden en hoop ik meer tijd voor jullie vrij te kunnen maken.

Niet los daarvan kan de band worden gezien met daarbij iedereen die daar ooit in heeft gespeeld of in had willen spelen, of die wij er graag in zouden zien spelen en de crew eromheen. Mijn onderzoek heeft onze internationale doorbraak enigszins vertraagd (nou, daar had ie dan weer geen tijd voor...), maar ik beloof deze achterstand binnenkort ruimschoots in te gaan halen!

Lieve Annie en Roelf, vaak was ik bezig met mijn onderzoek, jullie hebben daar altijd begrip voor gehad en mij uit de wind gehouden. Dank voor jullie onvoorwaardelijke steun.

Lieve familie, lieve papa, mama en Mariken. Nog iemand in de familie die een boekje heeft geschreven. Bedankt voor jullie steun, niet alleen voor, maar ook tijdens het onderzoek. Mariken, jij hebt mij leren ontwikkelen buiten de verplichte lesuren om. Het kan niet anders of dat heeft de voorzet gegeven tot hetgeen nu voor je ligt. Papa, een van mijn inspiratiebronnen, mama, een van mijn trouwste fans en natuurlijk schilderes van de omslag. Ik dank jullie voor jullie steun en jullie interesse en (fysieke en emotionele) inbreng. Jullie zijn mijn steun en toeverlaat en waardeer dat meer dan jullie weten. Ik hou van jullie.

Lieve Kina. Zonder mijn studie had ik jou niet gevonden, zonder jouw studie had ik mijn huidige opleiding niet gedaan. Zonder jou was ik niet waar en was ik niet wie ik nu ben. Kortom, jij hoort bij mij. En daar komt straks nog iemand anders bij. Zonder jou was ik al ik weet niet hoe vaak gestopt met mijn onderzoek, maar jij liet mij het belang maar ook de relativiteit ervan inzien. En dat is nog maar een klein deel van je invloed op mij. Hoe is het mogelijk dat andere mensen het volhouden zonder jou? Ik ben blij al bijna tien jaar met jou te mogen doorbrengen. Dit is nog maar het begin. Tijd om de bladzijde om te slaan, naar een nieuw hoofdstuk...ik hou van je.